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| (21) International Application Number: PCT/EP98/00497 (22) International Filing Date: 30 January 1998 (30.01.98) (30) Priority Data: 97101531.8 31 January 1997 (31.01.97) EP (34) Countries for which the regional or international application was filed: DE et al. (71) Applicant (for all designated States except US): BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH [DE/DE]; Gerhard-Gerdes-Strasse 19, D-37079 Göttingen (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): SCHLINGENSIEPEN, Karl-Hermann [DE/DE]; Pappelweg 3, D-37085 Göttingen (DE). BRYSCH, Wolfgang [DE/DE]; Calsowstrasse 56, D-37085 Göttingen (DE). (74) Agents: MEYERS, Hans-Wilhelm et al.; P.O. Box 10 22 41, D-50462 Cologne (DE). | | (81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DE, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i> |
| (54) Title: AN ANTISENSE OLIGONUCLEOTIDE PREPARATION METHOD (57) Abstract <p>A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of: selecting a target nucleic acid, if necessary elucidating its sequence; generating the antisense oligonucleotide with the proviso that: the oligonucleotide comprises at least 8 residues; the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases; the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG; the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG; and the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications: 3H-bond-R/3H-bond-R + 2H-bond-R \geq 0.29; and synthesizing the oligonucleotide thus generated in a per se known manner.</p> | | |

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An antisense oligonucleotide preparation method

The present invention is related to a method for the preparation of antisense oligonucleotides and to an oligonucleotide or functional or structural analogs or effective derivatives thereof, forming hydrogen bonds with deoxyribonucleic acids (DNA) and/or ribonucleic acids (RNA) or derivatives thereof including, but not limited to the formation of hydrogen bonds with the bases adenine (A), cytosine (C), guanine (G), uracil (U) or thymidine (T) contained in such molecules or forming hydrogen bonds with residues of a particular protein, such a molecule being capable of altering the expression structure or function, of a gene, an RNA molecule or a protein or altering the level of activity of a gene, an RNA molecule or a protein. Furthermore, the present invention is related to such nucleic acid or functional or structural analogs or effective derivatives thereof, coupled or mixed with folic acid, hormones, steroid hormones such as oestrogen, progesterone, corticosteroids, mineralocorticoids, androgens, peptides, proteoglycans, phospholipids, glycolipids and derivatives therefrom.

Furthermore, the invention is related to the use of said nucleic acids or functional or structural analogs or effec-

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tive derivatives thereof, for analyzing the functional properties of a particular gene, RNA, or protein by altering its activity, structure, function or altering its expression levels.

Furthermore, the invention is related to antisense nucleic acids, capable of modulating the expression or functional activity of proteins which regulate cell growth leading to augmentation, inhibition or modulation of cell growth or cell proliferation and/or the expansion of primary cells or stem cells, e.g. in culture or in the living organism.

Furthermore, the invention is related to a pharmaceutical composition comprising said nucleic acids or functional or structural analogs or effective derivatives thereof, hybridizing with an area of the messenger RNA (mRNA) or the DNA of a target gene or binding to a particular protein as well as the use of said nucleic acids, structural analogs and derivatives thereof for the manufacturing of a pharmaceutical composition for the treatment of diseases where the alteration of the structure function, activity or expression of a particular target gene, a particular target RNA or a particular target proteins activity leads to a therapeutic benefit related to the effect of the nucleic acid or derivative thereof.

Modulation of the expression of genes, RNA molecules or proteins or of their activity levels with nucleic acids or functional or structural analogs or effective derivatives thereof is a powerful means to study the function of the respective molecules. For example modulation, e. g. knockdown or increase of the expression of a particular protein can lead to the identification of its physiological as well as its pathophysiological roles in cultured cells as well as in living organisms in vivo.

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Furthermore, the aberrant expression or overexpression of genes, RNA molecules or proteins, the expression of foreign DNA, RNA or proteins e. g. derived from infectious organisms or the expression of mutated DNA, RNA and proteins is found in a variety of diseases. Downregulation of the expression or the activity of such DNA, RNA and/or proteins can lead to an inhibition of or to the reversal of pathological processes in which the expression of a particular DNA, RNA and/or protein plays a role. However, nucleic acids or derivatives thereof used for downregulation of DNA, RNA and/or protein expression are often ineffective and/or toxic to the cells or the organisms treated with such molecules.

An object of the present invention is to provide a method for designing and preparation of oligonucleotides or derivatives thereof which avoid the drawbacks of prior art, and give a reliable method for preparation of oligonucleotides having increased effectivity and/or reduced toxicity and/or reduced non-selective effects.

The object is attained by a method having the features of claims 1. Preferred embodiments of the method of the invention are those according to claims 2 to 7.

The method of the invention comprises the steps

- of selecting a target nucleic acid, if necessary elucidating its sequence
- generating the antisense oligonucleotide with the proviso that
 - the oligonucleotide comprises at least 8 residues,
 - the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,

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- the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG,
- the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and
- the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$\frac{3\text{H-bond-R}}{3\text{H-bond-R} + 2\text{H-bond-R}} \geq 0.29$$

- and synthesizing the oligonucleotide thus generated in a per se known manner.

The generated antisense oligonucleotide comprises at least 8 residues in order to have sufficient interaction with the target molecule and has preferably up to 30, more preferably up to 24 or most preferred up to 18 residues. Shorter chain length are preferred over longer ones to increase specificity and/or reduce non-specific effects.

The oligonucleotide comprises at maximum 12 elements which are capable of forming 3 hydrogen bonds each to cytosine bases. In case of generating an oligonucleotide an element is represented by a residue, thus a nucleotide of the oligo-

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nucleotide. In cases of generating a derivative an element is considered as a part of the molecule capable of forming hydrogen bonds. It is preferred that the oligonucleotide comprises at maximum 10 and more preferred at maximum 8 elements which are capable of forming 3 hydrogen bonds each to cytosine bases.

The generated antisense oligonucleotide preferably does not contain 4 or more consecutive guanine bases and does also not contain 2 or more series of 3 consecutive guanine bases.

Preferably, the ratio between residues forming 2 hydrogen bonds per residue (2H-bond-R) with their target molecule and those residues forming 3 hydrogen bonds per residue (3H-bond-R):

$$\frac{3\text{H-bond-R}}{\text{-----}} \\ 3\text{H-bond-R} + 2\text{H-bond-R}$$

is in the range of greater than 0.33 and smaller than 0.86, more preferably smaller than 0.79 and still more preferred smaller than 0.72.

In one embodiment the oligonucleotides generated by the method of the invention are modified for higher nuclease resistance than naturally occurring nucleotides. Methods for synthesizing oligonucleotides and derivatives thereof are known in the art, see for example "Oligonucleotides and Analogues", F. Eckstein (Ed.), 1991, IRL Press Oxford or "Protocols for Oligonucleotides and Analogs, Synthesis and Properties", Sudhir Agrawal (Ed.), 1993, Humana Press, Totowa, New Jersey.

Oligonucleotides of the invention may also contain RNA and DNA residues within their chains.

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The modifications can be made to the bases, the sugars or the linkages of the oligonucleotides. Preferably, the modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 - > P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar moiety or modifications of the bases. In a preferred embodiment the oligonucleotide has at least two different types of modifications and more preferably at least two different types of internucleotide linkages. In another preferred embodiment the oligonucleotides are linked to or mixed with folic acid, hormones such as steroid hormones or corticosteroids, peptides, proteoglycans, glycolipids, phospholipids or derivatives thereof.

Surprisingly the molecules, obtainable according to the method of the invention could strongly reduce or avoid toxicity and/or non-specific effects of such molecules and/or had significantly higher activity than sequences selected otherwise. Preferably, the molecules according to the invention have the following features: They do not contain four or more consecutive guanosine (N_aGGGN_b) or inosine ($N_aIIIIIN_b$) residues and the oligonucleotide does not contain two or more series of three or more consecutive guanosine residues ($N_aGGGN_cGGGN_b$) and does not contain two or more series of three or more consecutive inosine residues ($N_aIIIN_cIIIN_b$), wherein N_a , N_b , N_c represent independently oligonucleotides of any sequence having 0 to 20 residues.

In a preferred embodiment the molecule contains a minimum of 10 residues capable of forming either two or three hydrogen bonds per residue. Furthermore, the molecule contains a maximum of 24 consecutive residues linked by phosphorothioate linkages capable of forming either two or three hydrogen bonds per residue. In molecules according to the invention which contain more than 18 residues the additional

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linkages preferably consist of methylphosphonate linkages or phosphodiester linkages.

The chemical structures of antisense oligodeoxy-ribo-nucleotides are given in figure 1.

The chemical structures of antisense oligo-ribonucleotides are given in figure 2. The oligonucleotide is to be understood as a detail out of a longer nucleotide chain.

Of course, the oligonucleotides may be composed of elements of either figures.

In figures 1 and 2, lit. B means an organic base such as adenine (A), guanine (G), cytosine (C), inosine (I), uracil (U) and thymine (T) which are coupled to the deoxyribose. The linkages between the nucleotides are either phosphodiester bonds as in naturally occurring DNA or linkages spacing the nucleotides in such a way to allow hybridization with its target nucleic acid or binding to a protein in order to regulate its activity, such as e.g. phosphorothioate linkages, methylphosphonate linkages, phosphoramidate linkages or peptide linkages.

R_2 and R_3 represent further residues of the oligonucleotide or derivative.

R_4 represents OH or a modification such as a 2'-methoxy ethoxy derivative.

The modifications of the phosphodiester linkage, shown in figures 1 and 2 can be selected from, but are not limited to.

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1. Oligodeoxy-ribonucleotides or oligoribionucleotides substituted by

1.1 R1 = O

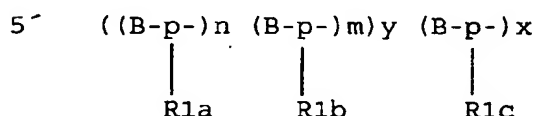
1.2 R1 = S

1.3. R1 = F

1.4. R1 = CH₃

1.4. R1 = OEt

2. Oligodeoxy-ribonucleotides where R1 is varied at the internucleotide phosphates within one oligonucleotide



where lit. p stands for the phosphodiester or the phosphoramidate linkage, modified by coupling to R1a, R1b or R1c or for a peptide linkage, or for linkages spacing the nucleotides in such a way to allow hybridization with its target nucleic acid or binding to a protein in order to regulate its activity, structure, function or expression level...

where lit. B = any deoxy-ribonucleotide or ribonucleotide, depending on gene sequence according to the invention.

n, m, x, y = integers 0 - 20

Preferred maximal length of the total number of bases is 30.

| | | | |
|-----|-----------------------------------|----------------------------------|----------------------------------|
| 2.1 | R _{1a} = S | R _{1b} =CH ₃ | R _{1c} =S |
| 2.2 | R _{1a} = S | R _{1b} =CH ₃ | R _{1c} =O |
| 2.2 | R _{1a} = S | R _{1b} =O | R _{1c} =S |
| 2.2 | R _{1a} = S | R _{1b} =O | R _{1c} =CH ₃ |
| 2.3 | R _{1a} = CH ₃ | R _{1b} =S | R _{1c} =CH ₃ |
| 2.4 | R _{1a} = CH ₃ | R _{1b} =S | R _{1c} =O |
| 2.5 | R _{1a} = CH ₃ | R _{1b} =O | R _{1c} =CH ₃ |
| 2.6 | R _{1a} = CH ₃ | R _{1b} =O | R _{1c} =S |

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| | | | |
|------|--------------|-----------------|-----------------|
| 2.7 | $R_{1a} = O$ | $R_{1b} = S$ | $R_{1c} = O$ |
| 2.8 | $R_{1a} = O$ | $R_{1b} = S$ | $R_{1c} = CH_3$ |
| 2.9 | $R_{1a} = O$ | $R_{1b} = CH_3$ | $R_{1c} = O$ |
| 2.10 | $R_{1a} = O$ | $R_{1b} = CH_3$ | $R_{1c} = S$ |

Preferably, the oligonucleotide comprises a minimum of 10 elements and a maximum of 24 elements capable of forming either 2 or 3 hydrogen bonds per element. The oligonucleotides of the invention can have modifications to the base, the sugar or the phosphate moiety. Preferred modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases. In a very preferred embodiment the antisense oligonucleotides comprise the sequences 41 to 73, 74 to 106, 154 to 172, 173 to 203, 298 to 380, 476 to 506, 519 to 556 and 597 to 641 of figure 3 and 1273 - 1764 of figure 5. A further aspect of the invention is the use of the oligonucleotides of the invention for the inhibition of the genes p53, rb, junD, junB, TGF- β 1, TGF- β 2 to influence cell proliferation, in particular of primary cell cultures such as liver cells, kidney cells, osteoclasts, osteoblasts and/or keratinocytes and/or cells of the blood lineage, such as bone marrow stem cells, and/or progenitor cells of red and white blood cells and/or organ stem cells.

The Sequences 41 - 73 and/or 74 - 106 and/or 154 - 203 and/or 519 - 556 and/or 597 - 641 and/or 1273 - 1277 and/or 1481 - 1490 and/or 1532 - 1549 and/or 1656 are useful for the treatment and/or prevention of immunosuppressive disorders including, but not limited to immunosuppression in neoplastic diseases - including gliomas and other brain tumors, sarcomas, carcinomas and lymphomas - and/or immunosuppression as side effect from drugs, including, but not limited to side effects from cytotoxic agents and/or immunosuppression in AIDS patients.

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In a further embodiment of the invention these sequences are also useful for the treatment and/or prevention of hyoproliferation of normal cells, including, but not limited to immune cells, bone marrow stem cells, endothelial cells, organ stem cells and proliferating cells of the intestine.

The Sequences 41 - 73 and/or 74 - 106 and/or 298 - 380 and/or 476 - 506 and/or 519 - 556 and/or 1273 - 1480 and/or 1596 - 1614 and/or 1657 - 1658 and/or 1690 and/or 1696 - 1712 and/or 1751 and/or 1753 - 1754 and/or 1757 are useful for the treatment and/or prevention of hyperproliferative disorders, including but not limited to brain tumors, sarcomas, carcinomas and lymphomas, restenosis, hyperplasia, pulmonary fibrosis, angiogenesis and psoriasis.

The Sequences 1278 - 1480 and/or 1491 - 1531 and/or 1582 - 1595 and/or 1615 - 1655 and/or 1691 - 1694 and/or 1697 - 1750 and/or 1759 - 1764 are useful for the treatment and/or prevention of diseases characterised by hyperfunction of the immune system and/or of inflammatory disorders and/or autoimmune disorders, including, but not limited to asthma (molecules according to the invention being applied by inhalation and/or by parenteral routes and/or orally), multiple sclerosis, inflammatory disorders of the intestine, including jejunitis, ileitis and/or colitis, as well as inflammatory disorders characterised by hyperproliferation and/or hyperfunction of cells of the eosinophilic lineage and/or glomerulonephritis and/or rejection of transplants.

The Sequences 476 - 506 and/or 1550 - 1581 and/or 1582 - 1595 and/or 1658 - 1689 and/or 1691 - 1694 and/or 1713 - 1752 are useful for the treatment and/or prevention of diseases associated with cell degeneration, including, but not limited to neurodegeneration, e.g. Alzheimer's diseases, Parkinson's, ischemic disorders, including myocardial ischemia and/or ischemia of the nervous system, including stroke.

A further aspect of the present invention is a medicament comprising an oligonucleotide according to the invention together with additives. The oligonucleotides of the invention can be used for the preparation of a medicament for the prevention or the treatment of neoplasm, hypoproliferation, hyperproliferation, degenerative diseases, neurodegenerative diseases, ischaemia, disorders of the immune system and/or infectious diseases and can be used for the analysis of gene function or drug target validation.

Molecules according to the invention can be used to study the function of target molecules and their encoded transcription and/or translation products, including RNA molecules and proteins. Downregulations of a protein or nucleic acid molecule using molecules according to the invention can be used to study the function of the molecule. It is also a feature of the invention that molecules according to the invention can be used to study whether modulation of the product has a desired effect, including therapeutic effects and to use this information to develop a different molecule, in order to modulate the function of the protein.

This includes, for example, drug target validation with a molecule according to the invention, in order to answer the question whether development of an agent capable of modulating the structure, function or expression of a potential target molecule, e. g. an agonist or antagonist of the target molecule has desired effect and may e. g. be of therapeutic or diagnostic use.

It is thus also a feature of the invention that molecules according to the invention can be used for drug target validation, including but not limited to studying whether modulation of a protein or nucleic acid molecule has a desired effect, including therapeutic effects and using this information to develop a compound, e. g. a therapeutic compound capable of modulating the structure, function or

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expression of the molecule the function of which was previously studied with molecules according to the invention.

Example 1

Treatment of Peripheral blood mononuclear cells with TGF- β 1 antisense phosphorothioate oligodeoxynucleotides:

Human peripheral blood mononuclear cells (PBMCs) produce transforming growth factor β 1 (TGF- β 1). The TGF- β 1 produced by these cells negatively regulates immune cell proliferation in an autologous manner. This autologous negative regulation of immune cell proliferation could be reversed by antisense TGF- β 1 molecules according to the invention, leading to stimulation of immune cell proliferation. In contrast to the molecules according to the invention, antisense molecules chosen conventionally, including that published by Hatzfeld et al. (1991) did not stimulate immune cell proliferation. Even more surprising, several sequences, chosen conventionally, even reduced immune cell proliferation.

Peripheral blood mononuclear cells (PBMCs) were isolated from venous blood of healthy donors by mixing with an equal volume of RPMI 1640 medium (Gibco) supplemented with 10 % fetal calf serum and 1 mM L-glutamine, followed by layering onto Ficoll-Hypaque (Pharmacia) gradients and centrifugation at 400 g for 30 min. PBMCs were removed from the plasma-Ficoll interface and washed in the above medium. Cells (2×10^4 in 100 μ l of medium) were plated into 96 well flat-bottom microtiter plates (Nunc) in serum supplemented complete medium. Cells were activated with 3 μ g/ml phytohemagglutinin and incubated with either no oligodeoxynucleotide (untreated control cells) or with 8 μ M of different antisense phosphorothioate oligodeoxynucleotides, complementary to different regions of the human TGF- β 1 mRNA for 4 days. Cells were then stained with trypan blue to determine cell viability and counted in a Neubauer counting chamber.

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Oligonucleotide sequences were either 33 sequences according to the invention, named sequences TGF- β 1-1 - TGF- β 1-33 or the TGF- β 1 antisense sequence from Hatzfeld et al. (1991), J. Exp. Med., 174, pp. 925 - 929 or 39 other conventionally chosen antisense sequences complementary to human TGF- β 1 mRNA, named N1 - N39 (see figure 3).

Surprisingly the molecules according to the invention were much more effective than antisense TGF- β 1 molecules that were chosen conventionally.

Sequences TGF- β 1-1 - TGF- β 1-33 (see figure 3) enhanced lymphocyte proliferation to between 135 and 213% of untreated controls. In contrast, treatment with the antisense sequence from document Hatzfeld et al. reduced proliferation to 62,8%.

Cells treated with the conventionally chosen TGF- β 1 antisense sequences N1 - N39 surprisingly not only failed to increase lymphocyte proliferation, but several of these sequences even revealed a marked inhibition of cell proliferation to between 51,4% and 77% of controls (sequences N1- N14, N20, N26 and N30 - N39). The antisense TGF- β 1 sequences N15:- N19; N21 - N25, N28 and N29 showed neither significant enhancement nor significant inhibition of cell proliferation with values between 94% and 103%. Sequence N27 showed slight toxicity with a reduction in cell proliferation to 88%.

Inhibition of cell proliferation by some of the TGF- β 1 sequences suggests that they may not be merely ineffective, but also toxic. Analysis of the 26 sequences N1- N14, N20, N26 and N30 - N39 revealed that 23 of them contained either 2 or more sequence motifs with three consecutive Gs (hereafter called GGG motif) or at least one motif with 4, 5, or 6 Gs (motifs GGGG, GGGGG, or GGGGGG). Analysis of the sequence from Hatzfeld et al., which also inhibited PBMC proliferation, surprisingly showed that it too contains a GGGGG plus a GGG motif. The 3 toxic sequences that contained

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neither 2 GGG motifs nor a motif of 4 or more consecutive Gs, i.e. sequences N8, N26, and N35 were found have a base content with 11 - 13 G-bases per sequence.

In contrast to the sequences from Hatzfeld et al., N1- N14, N20, N26 and N30 - N39 the sequences TGF- β 1-1 - TGF- β 1-33 showed a G-content of maximally 6 G-bases, no combination of two GGG motifs within a single sequence and no GGGG, GGGGG or GGGGGG motif. Since the TGF- β 1 mRNA contains more than 85 target regions for a GGG antisense motif and more than 34 target regions for a GGGG antisense motif, this finding in the sequences according to the invention was highly unlikely on a statistical basis.

The non-effective sequences N15 - N19, N21 - N25, N28 and N29 were found to contain a different base content from both the toxic and the effective sequences: They content of the bases A and T taken together (A/T-content) ranged from 14,3% to 28,5%. These sequences neither enhanced nor did they inhibit PBMC proliferation. Thus, they appeared to be neither effective nor toxic. In contrast to these non-effective sequences with an A/T content of 14,3% - 28,5%, the effective sequences TGF- β 1-1 - TGF- β 1-33 were found to have an A/T content of between 33% - 71,4%.

A further difference between the sequences of the invention and two thirds of the other sequences was found with respect to non-specific protein binding: Sequences from document Hatzfeld et al. and N1- N14, N20, N26 and N30 - N39 were found to show markedly enhanced non-specific protein binding compared to the sequences of the invention.

Sequences from Hatzfeld et al. (H) and N1 - N39 are shown in figure 3 as well as TGF- β 1 antisense sequences according to the invention.

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The finding that, while the sequences TGF- β 1-1 - TGF- β 1-33 stimulated proliferation of PBMC immune cells, the sequence from Hatzfeld et al. and sequences N1- N39 where either non-effective with little alteration in PBMC proliferation or had toxic effects and inhibited PBMC proliferation was extended to further antisense sequences both of TGF- β 2 and other genes as detailed in the following examples 2 - 7.

The sequences of the oligonucleotides related with TGF- β 1 are listed in figure 3 for the sake of ease of readability.

For certain applications, including, but not limited to application in dividing cells, including tumor cells, nucleic acid or functional or structural analogs or effective derivatives thereof according to the invention were coupled to folic acid, either at one of the carboxy-groups or at one of the nitrogen atoms of the folic acid.

Furthermore, for certain applications, nucleic acid or functional or structural analogs or effective derivatives thereof according to the invention are mixed with and/or coupled to hormones, steroid hormones such as oestrogen, progesterone, corticosteroids, mineralocorticoids, androgens, phospholipids, peptides, proteoglycans, glycolipids and derivatives therefrom. Preferably, a coupling occurs at R² and/or R³ of figures 1 and 2.

Example 2

p53 antisense nucleic acids (figure 3 shows the respective oligonucleotides)

p53 is a tumor suppressor gene that negatively regulates cell proliferation. Certain mutations in the gene can alter the function of p53 in such a way that it becomes an oncogene. The effects of p53 antisense oligodeoxynucleotides on cells

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containing wild type p53 was analyzed and subsequently also the effect of these sequences on cells with mutated p53.

In cells with wild type p53 effective antisense nucleic acids will lead to downregulation of the wild type p53 protein and thus to enhanced proliferation of the treated cells. Molecules according to the invention are named p53-1 - p53-33. Noneffective p53 antisense sequences were named p53-N-1 - p53-N-18. Toxic sequences, which inhibited proliferation instead of enhancing it as do effective p53 antisense sequences were named p53-T-1 - p53-T-29.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μ M concentration after 2 h.

Two assays to determine cell proliferation were performed:

- To determine 3H-thymidine incorporation, cells were incubated before harvesting with 0,15 μ Ci 3H-thymidine/well for 6 h. Cells were lysed by freezing, spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, only treatment of cells with antisense sequences according to the invention (p53-1 - p53-33) resulted in an increase in thymidine incorporation to between 3- and 9-fold.

In contrast, treatment with noneffective sequences (p53-N-1 - p53-N-18) did not result in significant alterations in thymidine incorporation.

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Furthermore, treatment with toxic antisense p53 sequences (p53-T-1- p53-T-29) resulted in a decrease in proliferation instead of an increase.

In summary, the 33 antisense sequences according to the invention resulted in effective downregulation of negative growth control by p53 and increased cell proliferation, while the 47 other antisense sequences had either no significant effect on cell proliferation or even suppressed cell proliferation.

Example 3

junB antisense nucleic acids (figure 3 shows the respective oligonucleotides)

junB and junD, two genes encoding transcription factors of the jun gene family are negative regulators of cell growth, like p53. The effects of different junB and junD antisense oligodeoxynucleotides was analyzed.

Effective junB and JunD antisense nucleic acids will lead to downregulation of the JunB and JunD proteins respectively and thus to enhanced proliferation of the treated cells. Antisense molecules according to the invention are named JunB-1 - JunB-19 and JunD-1 - JunD-31. Noneffective junB antisense sequences were named JunB-N-1 - JunB-N-57. Toxic sequences, which inhibited proliferation instead of enhancing it were named JunB-T-1- JunB-T-20 and JunD-T-1 - JunD-T-17.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μ M concentration after 2 h.

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Two assays to determine cell proliferation were performed:

- To determine ³H-thymidine incorporation, cells were incubated before harvesting with 0,15 μ Ci ³H-thymidine/well for 6 h. Cells were lysed by freezing, spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, again only treatment of cells with antisense sequences according to the invention (JunB-1 - JunB-19 and JunD1- JunD31) resulted in an increase in thymidine incorporation to between 2- and 7-fold.

In contrast, treatment with noneffective sequences (JunB-N-1 - JunB-N-57) did not result in significant alterations in thymidine incorporation.

Furthermore, treatment with toxic antisense junB or JunD sequences (JunB-T-1- JunB-T-20 and JunD-T-1 - JunD-T-17) resulted in a decrease in proliferation instead of an increase.

In summary, the 50 antisense sequences according to the invention resulted in effective downregulation of negative growth control by JunB and JunD, while the 94 other antisense sequences had either no significant effect on cell proliferation or were even toxic.

Example 4 (figure 3 shows the respective oligonucleotides)

erbB-2, is a transmembrane molecule with an intracellular tyrosine kinase activity that is amplified and/or overexpressed by carcinoma cells in a variety of neoplasms including breast cancer, lung cancer, oesophageal and gastric

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cancer, bile duct carcinoma, bladder cancer, pancreatic cancer and ovarian cancer.

In several of these tumors, an amplification and overexpression of the c-erbB-2 gene in the tumor tissue has been shown to correlate with a poor clinical prognosis. Overexpression of p185erbB-2 in non-small-cell lung carcinoma has been shown to impart resistance to a number of chemotherapeutic agents.

Effective erbB-2 antisense nucleic acids will lead to downregulation of the erbB-2 protein and in overexpressing tumor cell lines will lead to reduced cell proliferation of the treated cells. Antisense molecules according to the invention are named erbB-2-1 - erbB-2-83. Noneffective erbB-2 antisense sequences were named erbB-2-N-1 - erbB-2-N-95.

erbB-2 overexpressing SK-Br-3 human mammary carcinoma cells were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μ M concentration after 2 h.

To determine erbB-2 protein expression cells were harvested with a cell scraper and subjected to ELISA protein determination.

Only treatment of cells with antisense sequences according to the invention (erbB-2-1 - erbB-2-83) resulted in a significant reduction in erbB-2 protein expression by 40-95%.

In contrast, treatment with noneffective sequences (erbB-2-N-1 - erbB-2-N-95) did not result in significant alterations in erbB-2 protein expression.

To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

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Only treatment of cells with antisense sequences according to the invention (erbB-2-1 - erbB-2-83) resulted in a reduction in cell number by 35-70%.

In contrast, treatment with noneffective sequences (erbB-2-N-1 - erbB-2-N-95) did not result in significant alterations in cell proliferation.

erbB-2 antisense sequences were shown in figure 3-8 to 3-11

Example 5 (figure 3 shows the respective oligonucleotides)

The c-fos gene encodes an immediate early gene type transcription factor. Effective c-fos antisense nucleic acids will lead to downregulation of the c-Fos protein.

Antisense molecules according to the invention are named c-fos-1 - c-fos-31. Noneffective c-fos antisense sequences were named c-fos-N-1 - c-fos-N-12.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μ M concentration after 2 h.

Expression of the c-Fos protein was determined by ELISA in cell lysates.

Only treatment of cells with antisense sequences according to the invention (c-fos-1 - c-fos-31) resulted in a significant reduction in c-fos protein expression by 45-95%.

In contrast, treatment with noneffective sequences (c-fos-N-1 - c-fos-N-12) did not result in significant alterations in c-Fos protein expression.

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Example 6 (figure 3 shows the respective oligonucleotides)

TGF- β 2, like TGF- β 1 is a member of the transforming growth factor- β family of cytokines.

Overexpression of TGF- β 1 and TGF- β 2 is linked to malignant progression, immunosuppression and escape of the tumors from surveillance by the immune system.

Effective TGF- β 2 antisense nucleic acids will lead to downregulation of the TGF- β 2 growth factor.

Antisense molecules according to the invention are named TGF- β 2-1 - TGF- β 2-38. Noneffective TGF- β 2 antisense sequences were named TGF- β 2-N-1 - TGF- β 2-N-40.

TGF- β 2 overexpressing tumor cells were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μ M concentration after 2 h.

TGF- β 2 protein expression was determined by ELISA, both in the supernatant and in cell lysates.

Only treatment of cells with antisense sequences according to the invention (TGF- β 2-1 - TGF- β 2-38) resulted in a significant reduction in TGF- β 2 protein expression by 35-80%.

In contrast, treatment with noneffective sequences (TGF- β 2-N-1 - TGF- β 2-N-40) did not result in significant alterations in TGF- β 2 protein expression.

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Example 7 (figure 3 shows the respective oligonucleotides)

rb antisense nucleic acids

rb is a tumor suppressor gene that negatively regulates cell proliferation. The effects of rb antisense oligodeoxynucleotides on cells containing wild type rb was analyzed.

In cells with wild type rb effective antisense nucleic acids will lead to downregulation of the wild type rb protein and thus to enhanced proliferation of the treated cells. Molecules according to the invention are named rb-1 - rb-45. Noneffective rb antisense sequences were named -1 - rb-N-168. Toxic sequences, which inhibited proliferation instead of enhancing it as do effective rb antisense sequences were named rb-T-1- rb-T-16.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μ M concentration after 2 h.

Two assays to determine cell proliferation were performed:

- To determine 3H-thymidine incorporation, cells were incubated before harvesting with 0,15 μ Ci 3H-thymidine/well for 6 h. Cells were lysed by freezing, spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, only treatment of cells with antisense sequences according to the invention (rb-1 - rb-45) resulted in an increase in thymidine incorporation to between 2- and 6-fold.

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In contrast, treatment with noneffective sequences (rb-N-1 - rb-N-168) did not result in significant alterations in thymidine incorporation.

Furthermore, treatment with toxic antisense rb sequences (rb-T-1- rb-T-16) resulted in a decrease in proliferation instead of an increase.

In summary, the 45 antisense sequences according to the invention resulted in effective downregulation of negative growth control by rb and increased cell proliferation, while the 184 other antisense sequences had either no significant effect on cell proliferation or even suppressed cell proliferation.

Example 8

Oligonucleotide sequences according to the invention were synthesized with various different backbone modifications: Exemplary results are given below.

For the sequence

erbB-2-42: CATCTGGAACTTCCAGATG

the following chemical modifications were tested in erbB-2 overexpressing carcinoma cells:

1. S-ODN erbB-2-42 (i.e. all backbone linkages were thioate modifications).

C-pS-A-pS-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pS-T-pS-G

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2. Me-ODN/S-ODN/Me-ODN erbB-2-42 (i.e. Linkages at the 5' and 3' end were methylphosphonate linkages while linkages in the middle were thioate modifications as follows):

C-pMe-A-pMe-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-
pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-
pS-T-pS-C-pS-C-pS-A-pS-G-pMe-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pMe-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-
pS-T-pS-C-pS-C-pS-A-pMe -G-pMe-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pS-A-pS-A-pS-A-pS-C-pS-
T-pS-T-pS-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

3. Me-ODN / S-ODN erbB-2-42 (i.e. Linkages at the 5' end were methylphosphonate linkages while linkages at the 3' were thioate modifications as follows):

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pMe-A-pMe-A-pMe-A-pS-C-
pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pS-T-pS-G

4. S-ODN / Me-ODN erbB-2-42 (i.e. Linkages at the 5' end were methylphosphonate linkages while linkages at the 3' were thioate modifications as follows):

C-pS-A-pS-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pMe-C-pMe-T-
pMe-T-pMe-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

5. Me-ODN erbB-2-42 (i.e. linkages methylphosphonate linkages):

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pMe-A-pMe-A-pMe-A-C-
pMe-T-pMe-T-pMe-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

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6. pN/S-ODN/pN erbB-2-42 (i.e. Linkages at the 5' and 3' end were phosphoramidate linkages while linkages in the middle were thioate modifications as follows):

C-pN-A-pN-T-pS -C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-
T-pS-C-pS-C-pS-A-pS-G-pS-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-
T-pS-C-pS-C-pS-A-pS-G-pN-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pN -T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-
T-pS-C-pS-C-pS-A-pN -G-pN-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pN -T-pN -G-pN -G-pS-A-pS-A-pS-A-pS-C-pS-T-
pS-T-pS-C-pN -C-pN-A-pN -G-pN-A-pN-T-pN-G

where

pS stands for substitution of one of the non-bridging oxygen atoms of the backbone linkage with a sulfur atom, while pMe stands for substitution of one of the non-bridging oxygen atoms of the backbone linkage with a methyl group.

pN stands for a N3'→P5' phosphoramidate linkage.

Also a combination of linkages $(N-pS-N-pO-N-pO-N)_n-[pS-N]_m$ wherein $n = 1 - 10$ and $m = 0 - 6$ where N stand for any nucleotide or structural or functional analog or derivative thereof.

While the Me-ODN backbone modification strongly reduced the erbB-2 activity of the erbB-2-42 sequence to less than 20%, backbone modifications 1.-4. had strong erbB-2 inhibitory capacity with an inhibition of erbB-2 protein expression by between 78% and 89% at 2 μ M concentration at 48 h after the beginning of treatment of overexpressing carcinoma cells. While the pure S-ODN had the highest suppression capacity with 89%, the Me-ODN/S-ODN/Me-ODN as well as the Me-ODN/S-ODN

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and S-ODN/Me-ODN and pN/S-ODN/pN, displayed reduced protein binding and when tested for complement activation, showed reduced complement activation. These characteristics are advantageous for certain applications e.g. intravenous systemic application in vivo.

Example 9

Similar effects were obtained when testing other sequences according to the invention with the above backbone modifications.

Inhibition of TGF-beta-1 gene expression with the effective sequences for TGF-beta-1 according to the invention was highest with S-ODN and the Me-ODN/S-ODN/Me-ODN backbone modifications and lowest with the Me-ODN modification, while protein binding and complement activation were reduced in sequences containing Me-ODN linkages.

Example 10

Surprisingly, effectivity of sequences according to the invention was significantly improved in various cell types by coupling nucleic acids according to the invention to folic acid:

erbB-2 inhibitory capacity which was relatively low after 24 h compared to 48 h with an inhibition of erbB-2 protein synthesis by 24-37% was markedly increased by coupling sequences according to the invention to folic acid to 48-62% at 2 μ M concentration 24 h after the beginning of treatment of overexpressing carcinoma cells.

Similar effects were achieved by coupling sequences according to the invention to folic acid derivatives including aminopterin and amethopterin.

Example 11

Surprisingly, effectivity of sequences according to the invention was strongly improved by coupling oligonucleotides according to the invention to cortisol:

Cellular uptake and inhibitory capacity of sequences according to the invention including sequences for TGF-beta-1, TGF-beta-2, c-fos, p53, erbB-2, rb, c-fos, junB, junD, c-jun, MIP-1 alpha, JAK-2, bcl-2 and were markedly increased by coupling cortisol either to the 3' or 5' hydroxyl groups of oligonucleotide sequences according to the invention.

Example 12

Effectivity of sequences according to the invention was also strongly improved in various cell types by coupling nucleic acids according to the invention to or mixing them with other steroid hormones and their derivatives, including oestrogens, anti-oestrogens, prednisone, prednisolone, androgens, anti-androgens, gestagens like progesterone as well as peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.

Androgens, particularly androstendion and testosterone, as well as anti-androgens, including cyproteronacetate, flutamide, anandron, linked to the nucleic acids increased effectiveness of the molecules in various cell types including prostatic carcinoma cells.

Oestrogens, anti-oestrogens and their derivatives, including fosfestrol, toremifen, ethinyloestradiol, diethylstilboestole and the oestradiol derivatives oestradiol-benzoate, oestradiol-valerate and oestradiol-undecylate, as well as progesterone and its derivatives, including medroxyprogesteroneacetate and megestrolacetate linked to the oligonucleotides strongly enhanced activity of the molecules according

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to the invention in various cell types including mammary carcinoma cells.

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C l a i m s

1. A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of

- selecting a target nucleic acid, if necessary elucidating its sequence
- generating the antisense oligonucleotide with the proviso that
 - the oligonucleotide comprises at least 8 residues,
 - the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,
 - the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG,
 - the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and
 - the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$3\text{H-bond-R}$$

$$\geq 0.29$$

$$3\text{H-bond-R} + 2\text{H-bond-R}$$

- and synthesizing the oligonucleotide thus generated in a per se known manner.

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2. The method according to claim 1, wherein the generated oligonucleotide complies with the following specification

$$\frac{3\text{H-bond-R}}{3\text{H-bond-R} + 2\text{H-bond-R}} = 0.33 \text{ to } 0.86$$

3. The method according to any one of the claims 1 or 2, wherein the generated oligonucleotides are modified for higher nuclease resistance than naturally occurring oligo- or polynucleotides.
4. The method according to claim 3, wherein the generated oligonucleotides are modified at the bases, the sugars or the linkages of the oligonucleotides, preferably by phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.
5. The method according to claim 3 and/or 4, wherein the oligonucleotide has at least two different types of modifications.
6. The method according to any one of the claims 1 to 5, wherein the oligonucleotides are reacted with folic acid, hormones such as steroid hormones or corticosteroides or derivatives thereof by linking the oligonucleotides covalently to or mixing with folic acid, hormones such as steroid hormones or corticosteroides, peptides, proteoglycans, glycolipids or phospholipids.

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7. An antisense oligonucleotide or derivative thereof obtainable according to the method according to any one of the claims 1 to 6 except oligonucleotides represented by Fig. 4.
8. The oligonucleotide or derivative of claim 7, which does not contain four or more consecutive guanosine (N_aGGGGN_b) or inosine ($N_aIIIIIN_b$) residues and the oligonucleotide does not contain two or more series of three or more consecutive guanosine residues ($N_aGGGN_cGGGN_b$) and does not contain two or more series of three or more consecutive inosine residues ($N_aIIIN_cIIIN_b$), wherein N_a , N_b , N_c represent independently nucleotides or oligonucleotides or derivatives thereof having 0 to 20 residues.
9. The oligonucleotide or derivative of claims 7 and/or 8, comprising a minimum of ten elements and a maximum of 24 elements capable of forming either two or three hydrogen bonds per element.
10. The oligonucleotide or derivative according to any one of the claims 7 to 9, having modifications at the bases, the sugars or the phosphate moieties of the oligonucleotides.
11. The oligonucleotide or derivative of any one of the claims 7 to 10, wherein the modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.

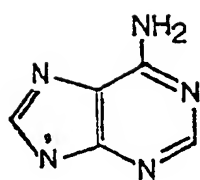
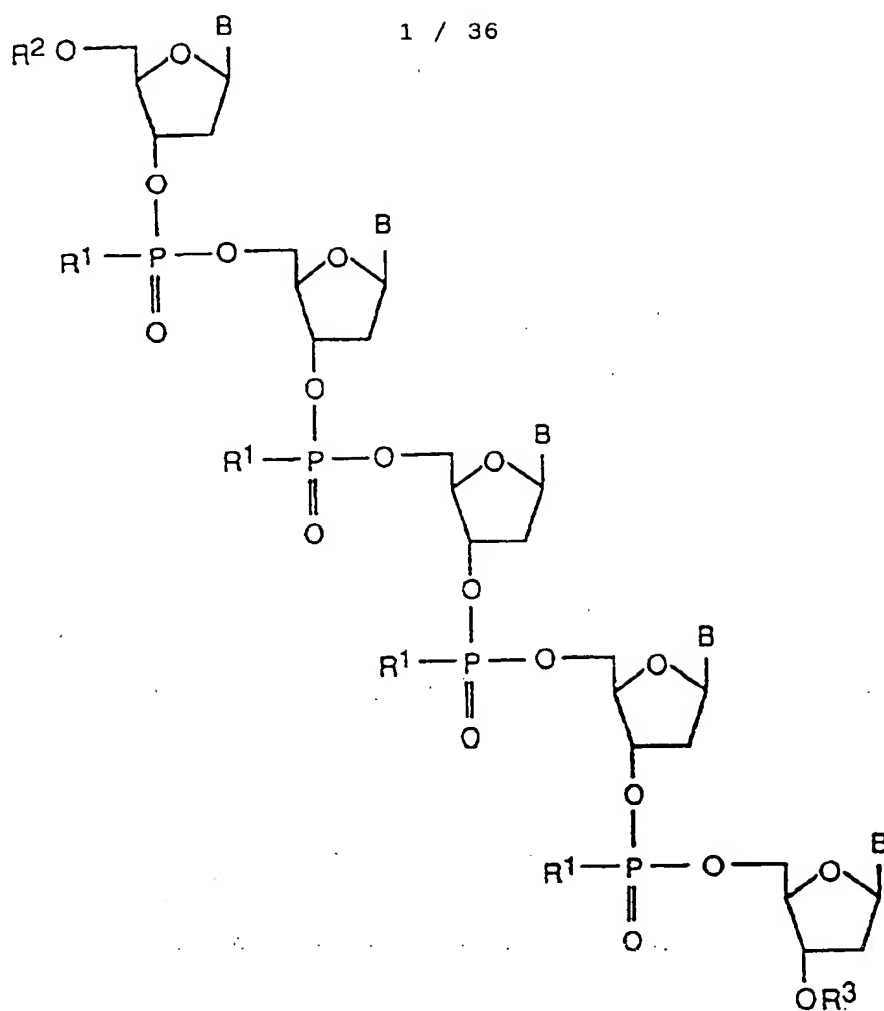
- 32 -

12. The oligonucleotide or derivative of any one of the claims 7 to 11 coupled to or mixed with folic acid, hormones, steroid hormones such as oestrogene, progesterone, corticosteroids, mineral corticoids, peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.
13. The oligonucleotide according to any one of the claims 7 to 12, wherein the antisense oligonucleotide against the TGF- β 1 gene comprise the sequences 41 to 73 of Fig. 3, the oligonucleotides against the gene p53 comprising the sequences 74 to 106 of Fig. 3, the antisense oligonucleotides against junB comprising the sequences 154 to 172 of Fig. 3, the antisense oligonucleotides against junD comprising the sequences 173 to 203 of Fig. 3, the antisense oligonucleotides against the erbB-2 gene comprise the sequences 298 to 380 of Fig. 3, the antisense oligonucleotides against c-fos genes comprise the sequences 476 - 506 of Fig. 3; the antisense oligonucleotides against the gene TGF- β 2 comprise the sequences 519 to 556 of Fig. 3 as well as the antisense oligonucleotides against the gene rb comprise the sequences 597 to 641 of Fig. 3.; as well as sequences 1273 to 1764. of Fig. 5.
14. A composition comprising an oligonucleotide or derivative according to any one of the claims 7 to 13 for the manufacturing of a medicament or a composition for the inhibition of the genes p53, rb, junD, junB, TGF- β 1, TGF- β 2 to influence cell proliferation, in particular of primary cell cultures such as liver cells, kidney cells, osteoclasts, osteoblasts and/or keratinocytes and/or cells of the blood lineage, such as bone marrow stem cells, and/or progenitor cells of red and white blood cells.

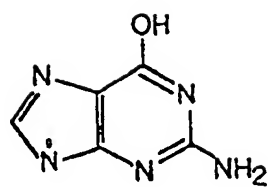
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15. A medicament comprising an oligonucleotide according to any one of the claims 7 to 13 together with additives.
16. The use of the oligonucleotides according to any of the claims 7 to 13 for the preparation of a medicament for the prevention or the treatment of neoplasm, hypoproliferation, hyperproliferation, degenerative diseases, neurodegenerative diseases, ischaemia, disorders of the immune system and/or infectious diseases, and/or metabolic dysfunctions.
17. The use of the oligonucleotides according to any one of the claims 7 to 13 for the analysis of gene function or drug target validation.

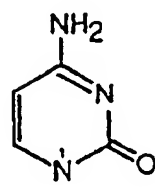
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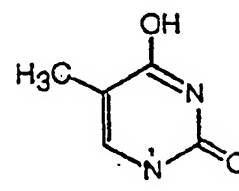
Adenine



Guanine



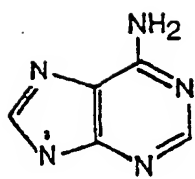
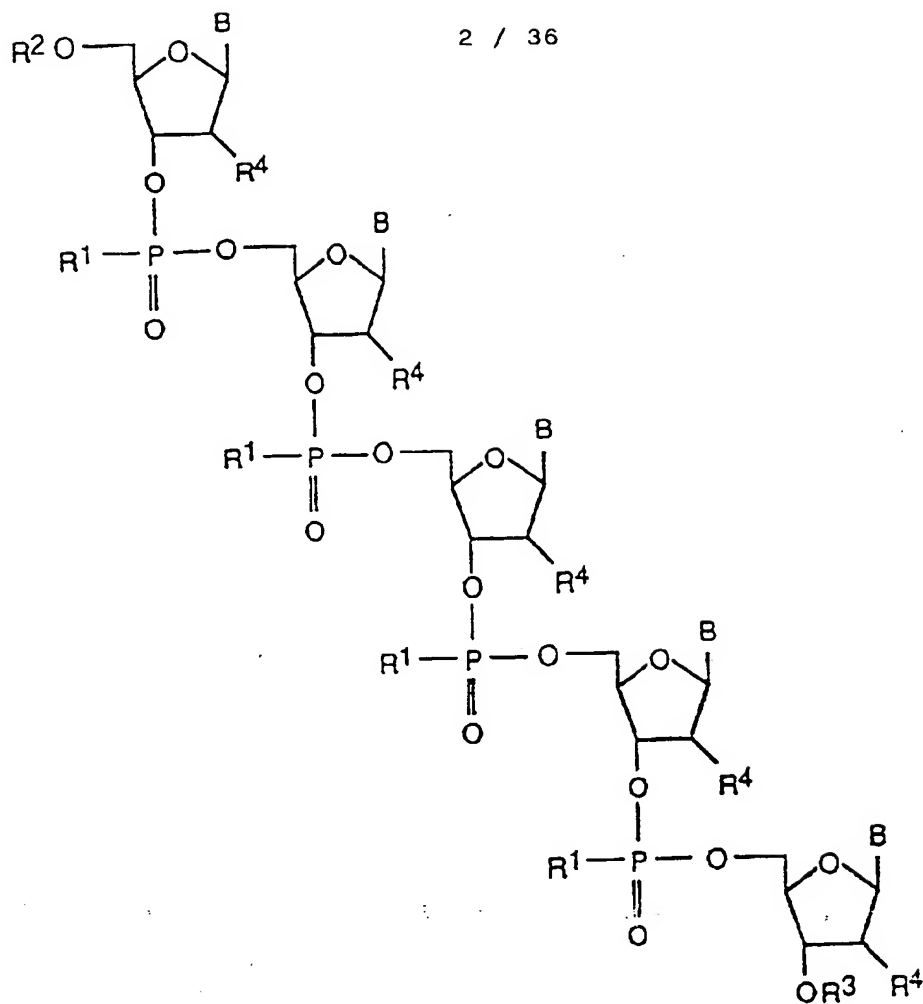
Cytosine



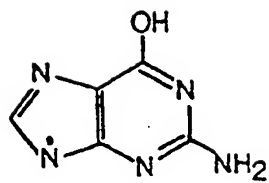
Thymine

Fig. 1

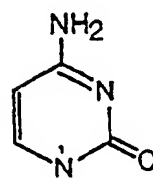
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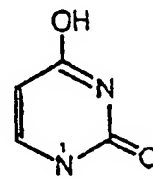
Adenine



Guanine



Cytosine



Uracil

FIG. 2

| | | |
|-----|------------------------|-----------------------------|
| 1. | A3 | CCCGGAGGGCGGCATGGGGGA |
| 2. | N1 | CCTCAGGGAGAAGGGCGC |
| 3. | N2 | GTAGGAGGGCCTCGAGGG |
| 4. | N3 | CTGCAGGGGCTGGGGGTC |
| 5. | N4 | AGGGCTGGTGTGGTGGGG |
| 6. | N5 | GGCATGGGGGAGGCGGCG |
| 7. | N6 | CCGGAGGGCGGCATGGGG |
| 8. | N7 | GGGGGGCTGGCGAGCCGC |
| 9. | N8 | GGACAGGATCTGGCCGCGGATGG |
| 10. | N9 | CCCCCTGGCTCGGGGGGC |
| 11. | N10 | GGGCCGGGCGGCACCTCC |
| 12. | N11 | GGGCAGCGGGCCGGGCGG |
| 13. | N12 | ACGGCCTCGGGCAGCGGG |
| 14. | N13 | GGGTGCTGTTGTACAGGG |
| 15. | N14 | GGGTTTCCACCATTAGCACGCGGG |
| 16. | N15 | TCATAGATTTCGTT |
| 17. | N16 | TTGTCATAGATT |
| 18. | N17 | AAGAACATATATATG |
| 19. | N18 | AAGAACATATATAT |
| 20. | N19 | TTGAAGAACATATATA |
| 21. | N20 | CCGGGAGAGCAACACGGG |
| 22. | N21 | ACTTTTAACTTGA |
| 23. | N22 | ATTGTTGCTGTATTT |
| 24. | N23 | ATTGTTGCTGTATT |
| 25. | N24 | AATTGTTGCTGTATT |
| 26. | N25 | AATTGTTGCTGTAT |
| 27. | N26 | GGCGAGTCGCTGGGTGCCAGCAGCCGG |
| 28. | N27 | GGCGAGTCGCTGGG |
| 29. | N28 | ACATCAAAAGATAA |
| 30. | N29 | TGACATCAAAAGAT |
| 31. | N30 | GGGCCCTCTCCAGCGGGG |
| 32. | N31 | GGGCTCGGGCGGTGCCGGG |
| 33. | N32 | GGGGCAGGGCCCGAGGCA |
| 34. | N33 | GGCTCCAAATGTAGGGGC |
| 35. | N34 | CGGGTTATGCTGGTTGTACAGGGG |
| 36. | N35 | CGGCGCCGCGAGGCGCCCGGG |
| 37. | N36 | GGGGCGGGGCGGGACC |
| 38. | N37 | GGGCGGGGCGGGGCGGGG |
| 39. | N38 | GGGCGGGGTGGGGCCGGG |
| 40. | N39 | GGGCAAGGCAGCGGGGCGGGG |
| 41. | TGF- B 1-1 | CGGTAGCAGCAGCG |
| 42. | TGF- B 1-2 | CCAGTAGCCACAGC |
| 43. | TGF- B 1-3 | GCAGGTGGATAGTCC |
| 44. | TGF- B 1-4 | CTTGCAGGTGGATAG |
| 45. | TGF- B 1-5 | CGATAGTCTTGCAGG |
| 46. | TGF- B 1-6 | CCATGTCGATAGTCTTGC |
| 47. | TGF- B 1-7 | CTCGATGCGCTTCCG |
| 48. | TGF- B 1-8 | CCTCGATGCGCTTCC |
| 49. | TGF- B 1-9 | GGATGGCCTCGATGC |
| 50. | TGF- B 1-10 | GGACAGGATCTGGCC |
| 51. | TGF- B 1-11 | CGCAGCTTGGACAGG |
| 52. | TGF- B 1-12 | GAGCCGCAGCTTGG |
| 53. | TGF- B 1-13 | CGAGCCGCAGCTTG |
| 54. | TGF- B 1-14 | ACCTCCCCCTGGCT |
| 55. | TGF- B 1-15 | CCACCATTAGCACG |
| 56. | TGF- B 1-16 | GAACCTTGTCATAGATTTC |
| 57. | TGF- B 1-17 | GCTGTGTGTACTCTGC |
| 58. | TGF- B 1-18 | GCTCCACGTGCTGC |
| 59. | TGF- B 1-19 | GAATTGTTGCTGTATTTTC |
| 60. | TGF- B 1-20 | GCCAGGAATTGTTGC |
| 61. | TGF- B 1-21 | GTGACATCAAAAGATAAC |
| 62. | TGF- B 1-22 | GGCTCAACCACTGCC |
| 63. | TGF- B 1-23 | GCTGTACAGGAGC |
| 64. | TGF- B 1-24 | CCTGCTGTACAGG |
| 65. | TGF- B 1-25 | GCAGTGTGTTATCCCTGC |
| 66. | TGF- B 1-26 | GCAGTGTGTTATCCC |

Fig. 3 - 1

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| | | |
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| 67. | TGF-β1-27 | CCAGGTCACCTCGG |
| 68. | TGF-β1-28 | GCCATGAATGGTGGC |
| 69. | TGF-β1-29 | GCCATGAATGGTGG |
| 70. | TGF-β1-30 | CCATGAGAAGCAGG |
| 71. | TGF-β1-31 | GGAAGTCAATGTACAGC |
| 72. | TGF-β1-32 | CCACGTAGTACACGATGG |
| 73. | TGF-β1-33 | GCACTTGCAGGAGC |
| 74. | p53-1 | CCATGGCAGTGACC |
| 75. | p53-2 | GGCTCCTCCATGGC |
| 76. | p53-3 | GCTAGGATCTGACTGC |
| 77. | p53-4 | CCTGACTCAGAGGG |
| 78. | p53-5 | GGTCTGAAAATGTTTCC |
| 79. | p53-6 | CCATTGCTTGGGACGG |
| 80. | p53-7 | GCATCAAATCATCC |
| 81. | p53-8 | CCATTGTTCAATATCG |
| 82. | p53-9 | GGTCTTCAGTGAACC |
| 83. | p53-10 | GGAGCTTCATCTGGACC |
| 84. | p53-11 | CCTCTGGCATTCTGG |
| 85. | p53-12 | AGGGACAGAAGATG |
| 86. | p53-13 | GTTTTCTGGGAAGG |
| 87. | p53-14 | GGTTTTCTGGGAAG |
| 88. | p53-15 | AGGTTTTCTGGGAAG |
| 89. | p53-16 | GTAGGTTTTCTGGG |
| 90. | p53-17 | GGTAGGTTTTCTGG |
| 91. | p53-18 | CCAGAATGCAAGAAGCC |
| 92. | p53-19 | GCTGTCCAGAAATGC |
| 93. | p53-20 | GCAAGTCACAGACTTGGC |
| 94. | p53-21 | CCACAGCTGCACAGG |
| 95. | p53-22 | GGTGTGGAATCAACC |
| 96. | p53-23 | GTCATGTGCTGTGA |
| 97. | p53-24 | CGCTATCTGAGCAGCG |
| 98. | p53-25 | CCAGTGTGATGATGG |
| 99. | p53-26 | CCAGTAGATTACCACTGG |
| 100. | p53-27 | GGCACAAACACGCACC |
| 101. | p53-28 | CCACGGATCTGAAGG |
| 102. | p53-29 | CGGAACATCTCGAAGCG |
| 103. | p53-30 | CCTCATTCAGCTCTCGG |
| 104. | p53-31 | CCTTGAGTTCCAAGG |
| 105. | p53-32 | CCTTTTGGACTTTCAGG |
| 106. | p53-33 | GGAGGTAGACTGACCC |
| 107. | p53-N-1 | AAAATGTTTCCT |
| 108. | p53-N-2 | TGAAAATGTTTC |
| 109. | p53-N-3 | CTGAAAATGTTT |
| 110. | p53-N-4 | TCTGAAAATGTTT |
| 111. | p53-N-5 | TCTGAAAATGTT |
| 112. | p53-N-6 | AAATCATCCATT |
| 113. | p53-N-7 | TTGTTCAATATC |
| 114. | p53-N-8 | ATTGTTCAATATC |
| 115. | p53-N-9 | ATTGTTCAATAT |
| 116. | p53-N-10 | CATTGTTCAATAT |
| 117. | p53-N-11 | CATTGTTCAATA |
| 118. | p53-N-12 | AAAAGTGTTCCT |
| 119. | p53-N-13 | ACATGAGTTTTTTAT |
| 120. | p53-N-14 | AACATGAGTTTTTTAT |
| 121. | p53-N-15 | ACATGAGTTTTTTA |
| 122. | p53-N-16 | AACATGAGTTTTTTA |
| 123. | p53-N-17 | AACATGAGTTTTTT |
| 124. | p53-N-18 | AAAACATCTTGT |
| 125. | p53-T-1 | CAGAGGGGGCTCGACGC |
| 126. | p53-T-2 | CTGACTCAGAGGGGGCTC |
| 127. | p53-T-3 | AGGGGGACAGAACC |
| 128. | p53-T-4 | TGGGACGGCAAGGGGGACAGAA |
| 129. | p53-T-5 | TGGGACGGCAAGGGGGA |

Fig. 3 - 2

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| | | |
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| 130. | p53-T-6 | GCCACGGGGGAGCA |
| 131. | p53-T-7 | GCAGGGGCCACGGGGGAG |
| 132. | p53-T-8 | AGGGGCCACGGGGG |
| 133. | p53-T-9 | CAGGGGCCACGGGG |
| 134. | p53-T-10 | GGTGCAGGGGCCACG |
| 135. | p53-T-11 | TGGTGCAGGGGCCCGCGG |
| 136. | p53-T-12 | GGGGCTGGTGCAGGGGCC |
| 137. | p53-T-13 | AGGGGGCTGGTGCAGGGG |
| 138. | p53-T-14 | GGGCTGGTGCAGGG |
| 139. | p53-T-15 | GAGGGGGCTGGTGCAG |
| 140. | p53-T-16 | AGGAGGGGGCTGGTG |
| 141. | p53-T-17 | GGGCCAGGAGGGGGCTGG |
| 142. | p53-T-18 | AGGGGCCAGGAGGGGGCT |
| 143. | p53-T-19 | GGGGCCAGGAGGGG |
| 144. | p53-T-20 | CAGGGGCCAGGAGGG |
| 145. | p53-T-21 | TCTGGGAAGGACAGA |
| 146. | p53-T-22 | TGAGGGCAGGGGAGTA |
| 147. | p53-T-23 | TTGAGGGCAGGGGAG |
| 148. | p53-T-24 | CGGGTGCCGGGCGGGGTG |
| 149. | p53-T-25 | CGGACGCGGGTGCCGGGCGGGGT |
| 150. | p53-T-26 | CGGGTGCCGGGCGGG |
| 151. | p53-T-27 | GGACGCGGGTGCCGGGCG |
| 152. | p53-T-28 | TGGGGGCAGCGCCTCACA |
| 153. | p53-T-29 | GGTGGGGGCAGCGCCT |
| | | |
| 154. | JunB-1 | CCATTTTAGTGCACATCCGG |
| 155. | JunB-2 | CCATTTTAGTGCACATCC |
| 156. | JunB-3 | GCTGTTCCATTTTAGTGC |
| 157. | JunB-4 | GTAGTCGTGTAGAG |
| 158. | JunB-5 | GTTTGTAGTCGTGTAG |
| 159. | JunB-6 | GTTTCAGGAGTTTGTAG |
| 160. | JunB-7 | CCAGCTCCGAAGAGG |
| 161. | JunB-8 | CGTCGTGTCGATCACG |
| 162. | JunB-9 | GGTAAAAGTACTGTCC |
| 163. | JunB-10 | GGCTTTGACAAAGCC |
| 164. | JunB-11 | CTTGTGCAGATCGTCCAG |
| 165. | JunB-12 | CGTGGTTTCATCTTGTGC |
| 166. | JunB-13 | CACGTGGTTTCATCTTGTG |
| 167. | JunB-14 | CCTCCTTGAAGGTGG |
| 168. | JunB-15 | CGCTCCACTTTGATGCG |
| 169. | JunB-16 | CCTTGTCTCCAGG |
| 170. | JunB-17 | GGTACTCGACAGCC |
| 171. | JunB-18 | CTGACGTGGGTCATG |
| 172. | JunB-19 | CCGTTGCTGACGTGG |
| | | |
| 173. | JunD-1 | CATCCTCCGCTCC |
| 174. | JunD-2 | GTTTCCATCCTCCG |
| 175. | JunD-3 | GGTGTTCATCCTCC |
| 176. | JunD-4 | GGTGTTCATCCTC |
| 177. | JunD-5 | GCTCAGCGCCTCATC |
| 178. | JunD-6 | CCTTCTTCATCATGCTGC |
| 179. | JunD-7 | CCTTCTTCATCATGCTG |
| 180. | JunD-8 | CCTTCTTCATCATGC |
| 181. | JunD-9 | GCGTCCTTCTTCATCATGC |
| 182. | JunD-10 | CCTGCTCACTCAGG |
| 183. | JunD-11 | CGCAGGCTTGAGCG |
| 184. | JunD-12 | GCCAGCTTCAGCAGC |
| 185. | JunD-13 | GGTGGTGACCAGCC |
| 186. | JunD-14 | CCTCGGCGAACTCC |
| 187. | JunD-15 | GCTTGTGTAAATCC |
| 188. | JunD-16 | GGTTCGTGCTTGTGTAAATCC |
| 189. | JunD-17 | GCTGCTCAGGTTGCG |
| 190. | JunD-18 | GAAGGCGACCGTCG |
| 191. | JunD-19 | CGAAGGCGACCGTC |
| 192. | JunD-20 | GCACCGTCTGTGGC |
| 193. | JunD-21 | CGTGTCCATGTGATGG |
| 194. | JunD-22 | CGTGTCCATGTGATG |

Fig. 3 - 3

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| | | |
|------|-----------|-----------------------|
| 195. | JunD-23 | GCGTGTCATGTCG |
| 196. | JunD-24 | CCAGCTTGCGCTTGC |
| 197. | JunD-25 | CGCTCCAGCTTGCG |
| 198. | JunD-26 | CGTGTCTGACTCTTGAG |
| 199. | JunD-27 | CGTGTCTGACTCTTG |
| 200. | JunD-28 | GCTGTGACGTGGC |
| 201. | JunD-29 | CGACTCAGTACGCC |
| 202. | JunD-30 | GCCATGCCCGACTC |
| 203. | JunD-31 | CCCTTGAGGTGGC |
| 204. | JunB-N-1 | TTTTAGTGACAT |
| 205. | JunB-N-2 | TGTTCCATTTTAGT |
| 206. | JunB-N-3 | AAAAAAAGTGAAG |
| 207. | JunB-N-4 | TACAAAAAAAGTG |
| 208. | JunB-N-5 | ATACAAAAAAAGT |
| 209. | JunB-N-6 | CATACAAAAAAAGT |
| 210. | JunB-N-7 | CATACAAAAAAAG |
| 211. | JunB-N-8 | GAAAAAAACATAC |
| 212. | JunB-N-9 | CAGAAAAAAACATAC |
| 213. | JunB-N-10 | CAGAAAAAAACAT |
| 214. | JunB-N-11 | TTCAATATGAATCG |
| 215. | JunB-N-12 | TATTCAATATGAATCG |
| 216. | JunB-N-13 | TATTCAATATGAATC |
| 217. | JunB-N-14 | TATTCAATATGAAT |
| 218. | JunB-N-15 | TATATTCAATATGAA |
| 219. | JunB-N-16 | TTATATTCAATATGA |
| 220. | JunB-N-17 | TATTATATTCAATATGA |
| 221. | JunB-N-18 | TTATATTCAATATG |
| 222. | JunB-N-19 | TATTATATTCAATATG |
| 223. | JunB-N-20 | ATTATATTCAATAT |
| 224. | JunB-N-21 | TATTATATTCAATAT |
| 225. | JunB-N-22 | ATATATTATATTCAATAT |
| 226. | JunB-N-23 | AAATATATTATATTCAATAT |
| 227. | JunB-N-24 | TATTATATTCAATA |
| 228. | JunB-N-25 | ATATATTATATTCAATA |
| 229. | JunB-N-26 | CAAAATATATTATATTCAATA |
| 230. | JunB-N-27 | TATATTATATTCAAT |
| 231. | JunB-N-28 | AATATATTATATTCAAT |
| 232. | JunB-N-29 | TATATTATATTCAA |
| 233. | JunB-N-30 | CAAAATATATTATATTCAA |
| 234. | JunB-N-31 | CAAAATATATTATATTCA |
| 235. | JunB-N-32 | CAAAATATATTATATTTC |
| 236. | JunB-N-33 | CACAAATATATTATATTTC |
| 237. | JunB-N-34 | AAATATATTATATT |
| 238. | JunB-N-35 | CAAAATATATTATATT |
| 239. | JunB-N-36 | CAAAATATATTATATT |
| 240. | JunB-N-37 | CACAAATATATTATATT |
| 241. | JunB-N-38 | CACAAATATATTAT |
| 242. | JunB-N-39 | TACACAAATATATTAT |
| 243. | JunB-N-40 | TACACAAATATATTA |
| 244. | JunB-N-41 | TAAATACACAAATATATT |
| 245. | JunB-N-42 | AATACACAAATATA |
| 246. | JunB-N-43 | GTTAAATACACAAATA |
| 247. | JunB-N-44 | TGTTAAATACACAA |
| 248. | JunB-N-45 | TTTAGAGACTAAGT |
| 249. | JunB-N-46 | ATAAACTCTTTAGA |
| 250. | JunB-N-47 | TAAAATAAACTCTTTAG |
| 251. | JunB-N-48 | TAAAATAAACTCTTTA |
| 252. | JunB-N-49 | TTAAAATAAACTCTTT |
| 253. | JunB-N-50 | CTTAAAATAAACTC |
| 254. | JunB-N-51 | TAAAAAGAACAAACA |
| 255. | JunB-N-52 | TAAAAAGAACAAAC |
| 256. | JunB-N-53 | CAATAAAAAGAACAA |
| 257. | JunB-N-54 | TCAATAAAAAGAACAA |
| 258. | JunB-N-55 | TCAATAAAAAGAAC |
| 259. | JunB-N-56 | TTCAATAAAAAGAA |
| 260. | JunB-N-57 | TAGATTCAATAAAAAGA |

Fig. 3 - 4

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| | | |
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| 261. | JunB-T-1 | TGGCGCGGGCGGGTAGC |
| 262. | JunB-T-2 | GGGCTGGCGCGGGCGGGTAG |
| 263. | JunB-T-3 | TCGGGGGCTGGCGCGGGCGGG |
| 264. | JunB-T-4 | TGGGTGCTGTGGTCGCGCGTTCTCGGG |
| 265. | JunB-T-5 | AGGGTCCCTGCGGGGCCG |
| 266. | JunB-T-6 | GGGAGGGTCCCTGCGGGG |
| 267. | JunB-T-7 | GGGAGGGTCCCTGCGG |
| 268. | JunB-T-8 | TGGGCCGGGTCCGC |
| 269. | JunB-T-9 | TCCCGGGGGTGTAG |
| 270. | JunB-T-10 | AGTACTGTCCCGGGGGTGT |
| 271. | JunB-T-11 | GGGACACGTTGGGGGGTG |
| 272. | JunB-T-12 | GCCGGGGGCCCGCGGTAGC |
| 273. | JunB-T-13 | CGGGCCAGCCGGGGC |
| 274. | JunB-T-14 | CGGGCCAGCCGGG |
| 275. | JunB-T-15 | GGGAGGTGGCTCCGGGCCGG |
| 276. | JunB-T-16 | AGGGCGGCGGTGTGGGA |
| 277. | JunB-T-17 | GGGTGGCCACCGGCGAAGGG |
| 278. | JunB-T-18 | AGGGGCAGGGACGT |
| 279. | JunB-T-19 | TAAAGGGCAGGGACGT |
| 280. | JunB-T-20 | AGGGGGTGTCCGTAAAGGG |
| 281. | JunD-T-1 | GGGGACGCGAACGTGCCGCCG |
| 282. | JunD-T-2 | CGGGGAACAAGCGGCCCGGGG |
| 283. | JunD-T-3 | GGCCGTGCGGGGGCG |
| 284. | JunD-T-4 | GCGGCCGTGCGGGGC |
| 285. | JunD-T-5 | AGGGGGGTAGGAGGCCGG |
| 286. | JunD-T-6 | GCGCTGGGGGGCGCC |
| 287. | JunD-T-7 | GGCCGTGCGGGGGT |
| 288. | JunD-T-8 | GGGGAGGCCAGCTTC |
| 289. | JunD-T-9 | GGCCGCCACCTTGGGG |
| 290. | JunD-T-10 | GCGGCCGCCCGCGGGG |
| 291. | JunD-T-11 | GGGCGCGGCCCGCGCGGGG |
| 292. | JunD-T-12 | GGGGTGGCGGCGGCGG |
| 293. | JunD-T-13 | GGGGGTGGCGGCGGC |
| 294. | JunD-T-14 | TGGGGCAGCAGCTGGCAG |
| 295. | JunD-T-15 | CGGGGCGCCACGACACC |
| 296. | JunD-T-16 | CGGGGCGCCACGACAC |
| 297. | JunD-T-17 | GGGCGCACCTCTCCAAGTCCGGGG |
| 298. | ErbB-2-1 | GCAGCAGTCAGTGG |
| 299. | ErbB-2-2 | CCATTGTCTAGCACGG |
| 300. | ErbB-2-3 | GGTCTCCATTGTCTAGC |
| 301. | ErbB-2-4 | GGTGGTATTGTTTCAGC |
| 302. | ErbB-2-5 | GCTGGATCAAGACCC |
| 303. | ErbB-2-6 | CCACAAAATCGTGTCC |
| 304. | ErbB-2-7 | CCTTCCACAAAATCGTGTCC |
| 305. | ErbB-2-8 | GGTTGTTCTTGTGG |
| 306. | ErbB-2-9 | CCTCTTGGTTGTGC |
| 307. | ErbB-2-10 | CCAGAGTCTCAAACACTTGG |
| 308. | ErbB-2-11 | GGTAACCTGTGATCTCTTCC |
| 309. | ErbB-2-12 | CCTGCAGTACTCGG |
| 310. | ErbB-2-13 | GGCAITCACATACTCC |
| 311. | ErbB-2-14 | GCAAACAGTGCCTGGC |
| 312. | ErbB-2-15 | CGCATCGTGTACTTCCG |
| 313. | ErbB-2-16 | GCACGTTCCGAGCG |
| 314. | ErbB-2-17 | GGTACCAGATACTCC |
| 315. | ErbB-2-18 | CCAGTGGAGACCTGG |
| 316. | ErbB-2-19 | CCTGAGGACACATCAGG |
| 317. | ErbB-2-20 | CCTCACTTGGTTGTGAGC |
| 318. | ErbB-2-21 | GGAAGATGTCCTTCC |
| 319. | ErbB-2-22 | GCACACTGCTCATGGC |
| 320. | ErbB-2-23 | GCTGTACCTCTTGG |
| 321. | ErbB-2-24 | CCTCTGCTGTACCC |
| 322. | ErbB-2-25 | CCACACATCACTCTGG |
| 323. | ErbB-2-26 | CCTCCTCTTCAGAGG |

Fig. 3 - 5

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| | | |
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| 324. | ErbB-2-27 | CCTTCTGGTTCACACTGG |
| 325. | ErbB-2-28 | CATGGTGCTCACTGCG |
| 326. | ErbB-2-29 | CTTGGTTGTGAGCG |
| 327. | ErbB-2-30 | GGACAGGCAGTCAC |
| 328. | ErbB-2-31 | GTCACCTCTTGGTTGTGC |
| 329. | ErbB-2-32 | CCAGAGTCTCAAACAC |
| 330. | ErbB-2-33 | CACATACTCCCTGG |
| 331. | ErbB-2-34 | GACCAGCAGTTCCG |
| 332. | ErbB-2-35 | GTGGGTGTCTATCAGTG |
| 333. | ErbB-2-36 | CCCTGGTAGAGGTG |
| 334. | ErbB-2-37 | CTCAAACACTTGGAGC |
| 335. | ErbB-2-38 | CACACATCACTCTGGTGG |
| 336. | ErbB-2-39 | GCACAGACAGTGCCG |
| 337. | ErbB-2-40 | CATGGCAGCAGTCAG |
| 338. | ErbB-2-41 | CTGCTCATGGCAGCAG |
| 339. | ErbB-2-42 | CATCTGGAAACTTCCAGATG |
| 340. | ErbB-2-43 | CTGGAAACTTCCAG |
| 341. | ErbB-2-44 | CATAACTCCACACATCACTC |
| 342. | ErbB-2-45 | CACCATAACTCCACACATC |
| 343. | ErbB-2-46 | CTGGTGGGTGAACC |
| 344. | ErbB-2-47 | CGGATTACTTGCAGG |
| 345. | ErbB-2-48 | CGCTAGGTGTCAGCG |
| 346. | ErbB-2-49 | GCCATCAGTATGC |
| 347. | ErbB-2-50 | GCATACACCAGTTCAGC |
| 348. | ErbB-2-51 | CCATCAAATACATCGG |
| 349. | ErbB-2-52 | CCAGCAGAAGTCAGG |
| 350. | ErbB-2-53 | GCTTCATGTCGTGC |
| 351. | ErbB-2-54 | GGTGAGTTCAGGTTTCC |
| 352. | ErbB-2-55 | CCACAAATCGTGTCTTGG |
| 353. | ErbB-2-56 | CCCTTACACATCGG |
| 354. | ErbB-2-57 | GCAGCTCACAGATGC |
| 355. | ErbB-2-58 | GCACTGGTAACTGC |
| 356. | ErbB-2-59 | CCTGGATATTGGCACTGG |
| 357. | ErbB-2-60 | CCAGCAAACCTCCTGG |
| 358. | ErbB-2-61 | GCAGAAATGCCAGGC |
| 359. | ErbB-2-62 | CCATTGTGCAGAAATTCG |
| 360. | ErbB-2-63 | CCCTGCAGTACTCGG |
| 361. | ErbB-2-64 | GGCATTACATACTCCC |
| 362. | ErbB-2-65 | GGTCAGGTTTCACACC |
| 363. | ErbB-2-66 | CCAGGTCCACACAGG |
| 364. | ErbB-2-67 | CCTTGTCTATCCAGG |
| 365. | ErbB-2-68 | GGATCCCAAAGACC |
| 366. | ErbB-2-69 | CCTCAACACTTTGATGG |
| 367. | ErbB-2-70 | GCTGTGTACCAGC |
| 368. | ErbB-2-71 | GGTCTAAGAGGCAGCC |
| 369. | ErbB-2-72 | GGCAATCTGCATACACC |
| 370. | ErbB-2-73 | CCTGTGTACGAGCC |
| 371. | ErbB-2-74 | CCATCCACTTGATGG |
| 372. | ErbB-2-75 | CCCACACAGTCACACC |
| 373. | ErbB-2-76 | CCATCGTAAGGTTTGG |
| 374. | ErbB-2-77 | CCTTTTCCAGCAGG |
| 375. | ErbB-2-78 | GGAGAATTCAGACACC |
| 376. | ErbB-2-79 | CCAAGTCTCTATTCTGG |
| 377. | ErbB-2-80 | CCATCAGTCTCAGAGG |
| 378. | ErbB-2-81 | CCTTTGAAGGTGCTGG |
| 379. | ErbB-2-82 | GGCATGGCAGGTTCC |
| 380. | ErbB-2-83 | CCTGGCATGGCAGG |
| 381. | ErbB-2-N-1 | AGATGTATAGGTAA |
| 382. | ErbB-2-N-2 | ATTTTCACATTCTC |
| 383. | ErbB-2-N-3 | AATTTTCACATTCTC |
| 384. | ErbB-2-N-4 | AATTTTCACATTCT |
| 385. | ErbB-2-N-5 | GAATTTTCACATT |
| 386. | ErbB-2-N-6 | GGAATTTTCACATT |
| 387. | ErbB-2-N-7 | AGATTTCTTTGTTG |
| 388. | ErbB-2-N-8 | AAGATTTCTTTGTTG |
| 389. | ErbB-2-N-9 | AAGATTTCTTTGTT |

Fig. 3 - 6

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| | | |
|------|-------------|-----------------------|
| 390. | ErbB-2-N-10 | TAAGATTTCTTTGTT |
| 391. | ErbB-2-N-11 | CTAAGATTTCTTTGTT |
| 392. | ErbB-2-N-12 | TAAGATTTCTTTGTT |
| 393. | ErbB-2-N-13 | CTAAGATTTCTTTGTT |
| 394. | ErbB-2-N-14 | CTAAGATTTCTTTG |
| 395. | ErbB-2-N-15 | TCTAAGATTTCTTT |
| 396. | ErbB-2-N-16 | GTCTAAGATTTCTTT |
| 397. | ErbB-2-N-17 | GTCTAAGATTTCTTT |
| 398. | ErbB-2-N-18 | TTCGTCTAAGATTT |
| 399. | ErbB-2-N-19 | ATTTTGACATGGTT |
| 400. | ErbB-2-N-20 | AATTTTGACATGGTT |
| 401. | ErbB-2-N-21 | AATTTTGACATGGT |
| 402. | ErbB-2-N-21 | TAATTTTGACATGGT |
| 403. | ErbB-2-N-23 | TAATTTTGACATGG |
| 404. | ErbB-2-N-24 | GTAATTTTGACATG |
| 405. | ErbB-2-N-25 | TGTAATTTTGACATG |
| 406. | ErbB-2-N-26 | TGTAATTTTGACAT |
| 407. | ErbB-2-N-27 | TCTGTAATTTTGACAT |
| 408. | ErbB-2-N-28 | CTGTAATTTTGACA |
| 409. | ErbB-2-N-29 | TCTGTAATTTTGACA |
| 410. | ErbB-2-N-30 | TCTGTAATTTTGAC |
| 411. | ErbB-2-N-31 | GTCTGTAATTTTGA |
| 412. | ErbB-2-N-32 | AAGTCTGTAATTTTGA |
| 413. | ErbB-2-N-33 | AGTCTGTAATTTTG |
| 414. | ErbB-2-N-34 | AAGTCTGTAATTTTG |
| 415. | ErbB-2-N-35 | AAGTCTGTAATTTT |
| 416. | ErbB-2-N-36 | GAAGTCTGTAATTTT |
| 417. | ErbB-2-N-37 | GAAGTCTGTAATTT |
| 418. | ErbB-2-N-38 | ATGTAGACATCAAT |
| 419. | ErbB-2-N-39 | ATCATCCAACATTT |
| 420. | ErbB-2-N-40 | AATCATCCAACATTT |
| 421. | ErbB-2-N-41 | AATCATCCAACATT |
| 422. | ErbB-2-N-42 | ACCATCAAATACAT |
| 423. | ErbB-2-N-43 | AAAAACGTCTTTGA |
| 424. | ErbB-2-N-44 | TTTTGTTCTTAGACA |
| 425. | ErbB-2-N-45 | TTTTGTTCTTAGAC |
| 426. | ErbB-2-N-46 | TAAACAGAAAAGCA |
| 427. | ErbB-2-N-47 | ACTAAACAGAAAAG |
| 428. | ErbB-2-N-48 | AAACTAAACAGAAAAG |
| 429. | ErbB-2-N-49 | AACTAAACAGAAAA |
| 430. | ErbB-2-N-50 | AACTAAACAGAAAA |
| 431. | ErbB-2-N-51 | AACTAAACAGAAAA |
| 432. | ErbB-2-N-52 | TAAAAACTAAACAGAAA |
| 433. | ErbB-2-N-53 | AAAACTAAACAGAA |
| 434. | ErbB-2-N-54 | GTAAAAACTAAACAGAA |
| 435. | ErbB-2-N-55 | AAAAACTAAACAGA |
| 436. | ErbB-2-N-56 | TAAAAACTAAACAGA |
| 437. | ErbB-2-N-57 | TAAAAACTAAACAG |
| 438. | ErbB-2-N-58 | GTAAAAACTAAACA |
| 439. | ErbB-2-N-59 | AAAAAGTAAAAACTAAACA |
| 440. | ErbB-2-N-60 | AGTAAAAACTAAAC |
| 441. | ErbB-2-N-61 | AAAAAAAAGTAAAAACTAAAC |
| 442. | ErbB-2-N-62 | AAGTAAAAACTAAA |
| 443. | ErbB-2-N-63 | AAAAAAAAGTAAAAACTAAA |
| 444. | ErbB-2-N-64 | AAAGTAAAAACTAA |
| 445. | ErbB-2-N-65 | AAAGTAAAAACTA |
| 446. | ErbB-2-N-66 | AAAAAAAAGTAAAAACTA |
| 447. | ErbB-2-N-67 | AAAAAGTAAAAACT |
| 448. | ErbB-2-N-68 | AAAAAAAAGTAAAAACT |
| 449. | ErbB-2-N-69 | AAAAAAAAGTAAAAAC |
| 450. | ErbB-2-N-70 | CAAAAAAAGTAAAAAC |
| 451. | ErbB-2-N-71 | AAAAAAAAGTAAAAA |
| 452. | ErbB-2-N-72 | CAAAAAAAGTAAAAA |
| 453. | ErbB-2-N-73 | AACAAAAAAGTAAAAA |
| 454. | ErbB-2-N-74 | AAACAAAAAAGTA |
| 455. | ErbB-2-N-75 | CAAAACAAAAAAGTA |
| 456. | ErbB-2-N-76 | CAAAACAAAAAAGT |

Fig. 3 - 7

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| | | |
|------|-------------|---------------------|
| 457. | ErbB-2-N-77 | CAAAACAAAAAAG |
| 458. | ErbB-2-N-78 | CTTTAAAAAACAAAAC |
| 459. | ErbB-2-N-79 | TCTTTAAAAAACAAA |
| 460. | ErbB-2-N-80 | GTCTTTAAAAAACAAA |
| 461. | ErbB-2-N-81 | GTCTTTAAAAAACAA |
| 462. | ErbB-2-N-82 | GTCTTTAAAAAAC |
| 463. | ErbB-2-N-83 | TTTATTTGTCCTTT |
| 464. | ErbB-2-N-84 | TCTTTATTTGTCCT |
| 465. | ErbB-2-N-85 | TATTTGCAAATGGA |
| 466. | ErbB-2-N-86 | TATATTTGCAAATGG |
| 467. | ErbB-2-N-87 | TATATTTGCAAATG |
| 468. | ErbB-2-N-88 | CAAAATATATTTGCAAATG |
| 469. | ErbB-2-N-89 | CAAAATATATTTGCAAT |
| 470. | ErbB-2-N-90 | CAAAATATATTTGCA |
| 471. | ErbB-2-N-91 | CAAAATATATTTGC |
| 472. | ErbB-2-N-92 | TTCCAAATATATTTG |
| 473. | ErbB-2-N-93 | TTTTCCAAATATATTT |
| 474. | ErbB-2-N-94 | GTTTTCCAAATATATT |
| 475. | ErbB-2-N-95 | GTTTTCCAAATAT |
| 476. | c-fos-1 | GGTTAGGCAAAGCC |
| 477. | c-fos-2 | CCGAGAACATCATCGTGG |
| 478. | c-fos-3 | CCGAGAACATCATCGTG |
| 479. | c-fos-4 | CCGAGAACATCATCG |
| 480. | c-fos-5 | CGTAGTCTGCGTTGAAGC |
| 481. | c-fos-6 | CCATGCTGGAGAAGG |
| 482. | c-fos-7 | CCGTGCAGAAGTCC |
| 483. | c-fos-8 | GGAATGAAGTTGGC |
| 484. | c-fos-8 | TGACCGTGGGAATG |
| 485. | c-fos-10 | TGGCAGTGACCGTG |
| 486. | c-fos-11 | AGATGGCAGTGACC |
| 487. | c-fos-12 | CGAGATGGCAGTGACC |
| 488. | c-fos-13 | CCAGCCACTGCAGG |
| 489. | c-fos-14 | GCACCAGCCACTGC |
| 490. | c-fos-15 | CCCTGGAGTAAGCC |
| 491. | c-fos-16 | GGAGATAACTGTTCCACC |
| 492. | c-fos-17 | GGAGATAACTGTTCC |
| 493. | c-fos-18 | CTTCTAGTTGGTCTG |
| 494. | c-fos-19 | CATCTTCTAGTTGG |
| 495. | c-fos-20 | TCTCATCTTCTAGTTGG |
| 496. | c-fos-21 | CTGCAAAGCAGACTTCTC |
| 497. | c-fos-22 | CCTTCAGCAGGTTGG |
| 498. | c-fos-23 | CCCAGGTCATCAGG |
| 499. | c-fos-24 | CCAGTCAGATCAAGG |
| 500. | c-fos-25 | GGTGAAGGCCCTCCTC |
| 501. | c-fos-26 | CAGGGTGAAGGCCTC |
| 502. | c-fos-27 | CCTGGATGATGCTGG |
| 503. | c-fos-28 | CCACTGTGCAGAGG |
| 504. | c-fos-29 | GGAGTACAGGTGACC |
| 505. | c-fos-30 | GCTCATGTGCTGCTGC |
| 506. | c-fos-31 | GGAAGGCTCATTGCTGC |
| 507. | c-fos-N-1 | TTTTCTCTTCTTCT |
| 508. | c-fos-N-2 | ATCTTATTCCTTTC |
| 509. | c-fos-N-3 | CATCTTATTCCTTT |
| 510. | c-fos-N-4 | TAGTTTTTCCTTCT |
| 511. | c-fos-N-5 | TCTAGTTTTTCCTT |
| 512. | c-fos-N-6 | AACTCTAGTTTTTC |
| 513. | c-fos-N-7 | GAACTCTAGTTTTT |
| 514. | c-fos-N-8 | TGAACTCTAGTTTTT |
| 515. | c-fos-N-9 | ATGAACTCTAGTTTTT |
| 516. | c-fos-N-10 | TGAACTCTAGTTTTT |
| 517. | c-fos-N-11 | ATGAACTCTAGTTTTT |
| 518. | c-fos-N-12 | ATGAACTCTAGTTTT |
| 519. | TGF-β2-1 | GCACACAGTAGTGC |

Fig. 3 - 8

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| | | |
|------|--------------------------|----------------------|
| 520. | TGF- 82 -2 | GCAGGATCAGAAAAGC |
| 521. | TGF- 82 -3 | GCAGGTAGACAGGC |
| 522. | TGF- 82 -4 | GCTGTGCTCAGGATCTGC |
| 523. | TGF- 82 -5 | GCAAGTCCCTGGTGC |
| 524. | TGF- 82 -6 | CCTGGAGCAAGTCC |
| 525. | TGF- 82 -7 | CGTAGTACTCTTCGTCG |
| 526. | TGF- 82 -8 | CGTAGTACTCTTCG |
| 527. | TGF- 82 -9 | GTAAACCTCCTTGG |
| 528. | TGF- 82 -10 | GTCTATTTTGTAAACCTCC |
| 529. | TGF- 82 -11 | GCATGTCTATTTTGTAAACC |
| 530. | TGF- 82 -12 | GGCATCAAGGTACCC |
| 531. | TGF- 82 -13 | GGCATCAAGGTACC |
| 532. | TGF- 82 -14 | GCCTTCACCAAATTGGAAGC |
| 533. | TGF- 82 -15 | GAGAATCTGATATAGCTC |
| 534. | TGF- 82 -16 | GGAGATGTTAAATCTTTGG |
| 535. | TGF- 82 -17 | GCTGTGATGTAGC |
| 536. | TGF- 82 -18 | CCAGGTTCTGTCCTTATGG |
| 537. | TGF- 82 -19 | CAGCAGGGACAGTG |
| 538. | TGF- 82 -20 | CTTGCTTCTAGTTCTTCAC |
| 539. | TGF- 82 -21 | GCCATCAATACCTGC |
| 540. | TGF- 82 -22 | GGTGCCATCAATACC |
| 541. | TGF- 82 -23 | CCACTGGTATATGTGG |
| 542. | TGF- 82 -24 | GGACTTTATAGTTTCTG |
| 543. | TGF- 82 -25 | CTCAAGTCTGTAGGAG |
| 544. | TGF- 82 -26 | GGTCTGTTGTGACTC |
| 545. | TGF- 82 -27 | CAATTATCCTGCACATTTT |
| 546. | TGF- 82 -28 | GCAGCAATTATCCTGC |
| 547. | TGF- 82 -29 | GGCAGCAATTATCC |
| 548. | TGF- 82 -30 | GGTTCGTGTATCCATTTCC |
| 549. | TGF- 82 -31 | GCACAGAAAGTTGGC |
| 550. | TGF- 82 -32 | CCAGCACAGAAGTTGG |
| 551. | TGF- 82 -33 | GTGCTGAGTGTCTG |
| 552. | TGF- 82 -34 | CCTGCTGTGCTGAGTG |
| 553. | TGF- 82 -35 | GCTCAGGACCCTGC |
| 554. | TGF- 82 -36 | GCAGCAAGGAGAAGC |
| 555. | TGF- 82 -37 | CCAATGTAGTAGAATGG |
| 556. | TGF- 82 -38 | GCTGCATTTGCAAG |
| 557. | TGF- 82 -N-1 | AAAAAAGAAATCAA |
| 558. | TGF- 82 -N-2 | AAAAAAGAAATCAA |
| 559. | TGF- 82 -N-3 | AAAAAAGAAATCAA |
| 560. | TGF- 82 -N-4 | TAAAAAAGAAATCAA |
| 561. | TGF- 82 -N-5 | ATAAAAAAGAAATCAA |
| 562. | TGF- 82 -N-6 | AATAAAAAAAGAAATCAA |
| 563. | TGF- 82 -N-7 | GAATAAAAAAAGAAAT |
| 564. | TGF- 82 -N-8 | AGAATAAAAAAAGAAAT |
| 565. | TGF- 82 -N-9 | CAGAATAAAAAA |
| 566. | TGF- 82 -N-10 | TCAGAATAAAAAA |
| 567. | TGF- 82 -N-11 | TTGTTTTTAAAGT |
| 568. | TGF- 82 -N-12 | AGTTGTTTTTAA |
| 569. | TGF- 82 -N-13 | AAGTTGTTTTTAA |
| 570. | TGF- 82 -N-14 | AAAGTTGTTTTTAA |
| 571. | TGF- 82 -N-15 | AAAAGTTGTTTTTAA |
| 572. | TGF- 82 -N-16 | AAAAAGTTGTTTTTAA |
| 573. | TGF- 82 -N-17 | AAAAAAGTTGTTTTTAA |
| 574. | TGF- 82 -N-18 | AAAAAAGTTGTTTTTAA |
| 575. | TGF- 82 -N-19 | AAAAAAGTTGTTTTTAA |
| 576. | TGF- 82 -N-20 | TTTTTAAAAAAGTG |
| 577. | TGF- 82 -N-21 | TTTTTTAAAAAAGTG |
| 578. | TGF- 82 -N-22 | ATTTTTTAAAAAAGTG |
| 579. | TGF- 82 -N-23 | CATTTTTTAAAAAAGT |
| 580. | TGF- 82 -N-24 | GCATTTTTTAAAAA |
| 581. | TGF- 82 -N-25 | TGCATTTTTTAAAAA |
| 582. | TGF- 82 -N-26 | AGCTTATTTTAAAT |
| 583. | TGF- 82 -N-27 | AAGCTTATTTTAAAT |
| 584. | TGF- 82 -N-28 | TAAGCTTATTTTAAAT |
| 585. | TGF- 82 -N-29 | TGTAATTATTAGAT |

Fig. 3 - 9

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| | | |
|------|-------------|----------------------|
| 586. | TGF-β2-N-30 | ATGTAATTATTAGAT |
| 587. | TGF-β2-N-31 | TGATGTAATTATTA |
| 588. | TGF-β2-N-32 | ATGATGTAATTATTA |
| 589. | TGF-β2-N-33 | ATGGTATTATATAA |
| 590. | TGF-β2-N-34 | TATGGTATTATATAA |
| 591. | TGF-β2-N-35 | TTATGGTATTATATAA |
| 592. | TGF-β2-N-36 | TTTATGGTATTATATAA |
| 593. | TGF-β2-N-37 | ATTTATGGTATTATATAA |
| 594. | TGF-β2-N-38 | AATCATATTAGAAA |
| 595. | TGF-β2-N-39 | TTACAATCATATTA |
| 596. | TGF-β2-N-40 | TTTACAATCATATTA |
| | | |
| 597. | rb-1 | GGCATGACGCCTTTCC |
| 598. | rb-2 | GCATGACGCCTTTC |
| 599. | rb-3 | GCCTGACGAGAGGC |
| 600. | rb-4 | CTCAAGCCTGACGAG |
| 601. | rb-5 | CCACAGTTCCTTTTTC |
| 602. | rb-6 | GCTGCAATAAAGATACAG |
| 603. | rb-7 | GCTGCAATAAAGATAC |
| 604. | rb-8 | GGACACTGATTTCATG |
| 605. | rb-9 | GCATTATCAACTTTGG |
| 606. | rb-10 | ACTTTTAGCACCAATG |
| 607. | rb-11 | CCAAGAACTTTTAGCACC |
| 608. | rb-12 | CCAGATCATCTTCC |
| 609. | rb-13 | AGTCAAGGACACATAG |
| 610. | rb-14 | TCTTTGAGCAACATGG |
| 611. | rb-15 | GGGTATAACAGCTG |
| 612. | rb-16 | GAGGTGAACCATTAATGG |
| 613. | rb-17 | TCTTCGTATCGTTTAG |
| 614. | rb-18 | TGTTGGATAGTGTTT |
| 615. | rb-19 | GTTGATCACTTGCTG |
| 616. | rb-20 | GGATTCCATTACTCG |
| 617. | rb-21 | GACATATGAAAAATGTTGTC |
| 618. | rb-22 | GCCAAATAAAGACATATG |
| 619. | rb-23 | CCAGAATCAAGATTCTG |
| 620. | rb-24 | CTGTTCCAGAATCAAG |
| 621. | rb-25 | GACAAATCTGTTCCAGAATC |
| 622. | rb-26 | GGAAAGACAAATCTGTTCC |
| 623. | rb-27 | GATTAAGAGGACAAGC |
| 624. | rb-28 | GGAAGATTAAGAGG |
| 625. | rb-29 | GCAGTGTGATTATTCTGG |
| 626. | rb-30 | GGAGAAAGATACATATCTG |
| 627. | rb-31 | GGAGATCTTACAGG |
| 628. | rb-32 | GCATTTGCAGTAGAATTAC |
| 629. | rb-33 | CAGTGAAAGAGAGG |
| 630. | rb-34 | GCTAGCCGATACAC |
| 631. | rb-35 | GGAAGATCCTTGTATGC |
| 632. | rb-36 | GCATGAGGAAGATCC |
| 633. | rb-37 | GGAGTCATTTTGTGTTG |
| 634. | rb-38 | CCAATTGATACTAAGATTC |
| 635. | rb-39 | TCTTTTGAGCACACG |
| 636. | rb-40 | CCTTCAGCACTTCTTTTG |
| 637. | rb-41 | GGTTGCTTCCTTCAGC |
| 638. | rb-42 | CAGTGGTTTAGGAG |
| 639. | rb-43 | CCTGAGATCCTCATTTT |
| 640. | rb-44 | CCAAGGTCCTGAGATCC |
| 641. | rb-45 | GGTGACACAGTGTCC |
| | | |
| 642. | rb-N-1 | TATCTTTAATTTCT |
| 643. | rb-N-2 | TCTTTTGAATATAA |
| 644. | rb-N-3 | TTCTTTTGAATATAA |
| 645. | rb-N-4 | TTTCTTTTGAATATAA |
| 646. | rb-N-5 | TTTTCTTTTGAATATAA |
| 647. | rb-N-6 | TTTTTCTTTTGAATATAA |
| 648. | rb-N-7 | ATTTCTATGTTTTT |
| 649. | rb-N-8 | TTAAAGAATTTATG |
| 650. | rb-N-9 | GTAAAGAATTTAT |

Fig. 3 - 10

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| | | |
|------|---------|--------------------------|
| 651. | rb-N-10 | AGTTAAAGAATTTAT |
| 652. | rb-N-11 | AAGTTAAAGAATTTAT |
| 653. | rb-N-12 | TAAGTTAAAGAATTTAT |
| 654. | rb-N-13 | TTTAGTAAGTTAAA |
| 655. | rb-N-14 | TTTAGTAAGTTAAA |
| 656. | rb-N-15 | ATTTCTTTTAGTAA |
| 657. | rb-N-16 | AATTTCTTTTAGTAA |
| 658. | rb-N-17 | ATCAATTTCTTTTA |
| 659. | rb-N-18 | TATCAATTTCTTTTA |
| 660. | rb-N-19 | AATATATAAGTTCA |
| 661. | rb-N-20 | AAATATATAAGTTCA |
| 662. | rb-N-21 | CAAAATATATAAGTT |
| 663. | rb-N-22 | TCAAATATATAAGTT |
| 664. | rb-N-23 | TGTCAAATATATAA |
| 665. | rb-N-24 | AATTTATTTTCAGTA |
| 666. | rb-N-25 | AATAAAAAATGTGAT |
| 667. | rb-N-26 | TAATAAAAAATGTGAT |
| 668. | rb-N-27 | TAGCTAATAAAAAAT |
| 669. | rb-N-28 | TTAGCTAATAAAAAAT |
| 670. | rb-N-29 | TTTAGCTAATAAAAAAT |
| 671. | rb-N-30 | AATAAAAAATAGTCAA |
| 672. | rb-N-31 | TAATAAAAAATAGTCAA |
| 673. | rb-N-32 | TTAATAAAAAATAGTCAA |
| 674. | rb-N-33 | TTTAATAAAAAATAGTCAA |
| 675. | rb-N-34 | GTTTAATAAAAAATAGT |
| 676. | rb-N-35 | AGTTTAATAAAAAATAGT |
| 677. | rb-N-36 | GAGTTTAATAAAAAATA |
| 678. | rb-N-37 | AGAGTTTAATAAAAAATA |
| 679. | rb-N-38 | AATAATTCTTGTAT |
| 680. | rb-N-39 | TATATTACATTCAT |
| 681. | rb-N-40 | ATCTATATTACATT |
| 682. | rb-N-41 | ATAAACATTTTTTCA |
| 683. | rb-N-42 | AAATAAACATTTTTTCA |
| 684. | rb-N-43 | AAATAAACATTTTTTCA |
| 685. | rb-N-44 | GAAATAAACATTTTTT |
| 686. | rb-N-45 | TGAAATAAACATTTTTT |
| 687. | rb-N-46 | TTGAAATAAACATTTTTT |
| 688. | rb-N-47 | TTTGAAATAAACATTTTTT |
| 689. | rb-N-48 | TTTTGAAATAAACATTTTTT |
| 690. | rb-N-49 | TTTTTGAAATAAACATTTTTT |
| 691. | rb-N-50 | ATTTTTGAAATAAACATTTTT |
| 692. | rb-N-51 | AATTTTTGAAATAAACATT |
| 693. | rb-N-52 | AAATTTTTGAAATAAACATT |
| 694. | rb-N-53 | AAAATTTTTGAAATAAACATT |
| 695. | rb-N-54 | TAAAATTTTTGAAATAAACATT |
| 696. | rb-N-55 | ATAAAATTTTTGAAATAAACATT |
| 697. | rb-N-56 | TATAAAATTTTTGAAATAAACATT |
| 698. | rb-N-57 | GTATAAAATTTTTGAAAT |
| 699. | rb-N-58 | GGTATAAAATTTTTT |
| 700. | rb-N-59 | AGGTATAAAATTTTTT |
| 701. | rb-N-60 | AAGGTATAAAATTTTTT |
| 702. | rb-N-61 | AAAGGTATAAAATTTTTT |
| 703. | rb-N-62 | AAAAGGTATAAAATTTTTT |
| 704. | rb-N-63 | TAAAAGGTATAAAATTTTTT |
| 705. | rb-N-64 | ATAAAAGGTATAAAATTTTTT |
| 706. | rb-N-65 | TTTAGAAAGATTTTT |
| 707. | rb-N-66 | AAGATAAAATTTCTT |
| 708. | rb-N-67 | TAAGATAAAATTTCTT |
| 709. | rb-N-68 | TTAAGATAAAATTTCTT |
| 710. | rb-N-69 | TTTAAGATAAAATTTCTT |
| 711. | rb-N-70 | TTTTAAGATAAAATTTCTT |
| 712. | rb-N-71 | TTTTTAAGATAAAATTTCTT |
| 713. | rb-N-72 | ATTTTTAAGATAAAATTTCTT |
| 714. | rb-N-73 | TATTTTTAAGATAAAATTTCTT |
| 715. | rb-N-74 | TTATTTTTAAGATAAAATT |
| 716. | rb-N-75 | TTTATTTTTAAGATAAAATT |
| 717. | rb-N-76 | CTTTATTTTTAAGATAAAAT |

Fig. 3 - 11

| | | |
|------|----------|-----------------------|
| 718. | rb-N-77 | TCTTTATTTTAAAGATAAAAT |
| 719. | rb-N-78 | ATCTTTATTTTAAAGATAAAA |
| 720. | rb-N-79 | ATCTTTATTTTAA |
| 721. | rb-N-80 | GATCTTTATTTTAA |
| 722. | rb-N-81 | AGATCTTTATTTTAA |
| 723. | rb-N-82 | TAGATCTTTATTTTAA |
| 724. | rb-N-83 | AATCATCATTAATT |
| 725. | rb-N-84 | AAATCATCATTAATT |
| 726. | rb-N-85 | AAAATCATCATTAATT |
| 727. | rb-N-86 | TAAAATCATCATTAATT |
| 728. | rb-N-87 | TTAAAATCATCATTAATT |
| 729. | rb-N-88 | TTTAAAATCATCATTAATT |
| 730. | rb-N-89 | ATTTAAAATCATCATTAATT |
| 731. | rb-N-90 | AATTTAAAATCATCATTAAT |
| 732. | rb-N-91 | GAATTTAAAATCAT |
| 733. | rb-N-92 | TGAATTTAAAATCAT |
| 734. | rb-N-93 | TTAAAATAGGAAAT |
| 735. | rb-N-94 | AATTTCTCTTAA |
| 736. | rb-N-95 | AAATTTCTCTTAA |
| 737. | rb-N-96 | TAAAATTTGAATG |
| 738. | rb-N-97 | CTAAAATTTGAAT |
| 739. | rb-N-98 | TTTGCTAAAATTTT |
| 740. | rb-N-99 | ATATGAAAAATGTT |
| 741. | rb-N-100 | TTTTAAATTAAGCA |
| 742. | rb-N-101 | TTGTAAAATCAAA |
| 743. | rb-N-102 | TTTGTA AAAATCAAA |
| 744. | rb-N-103 | TTTGATAAACTTT |
| 745. | rb-N-104 | ATGTTTTATCATTT |
| 746. | rb-N-105 | AATGTTTTATCATTT |
| 747. | rb-N-106 | AAATGTTTTATCATTT |
| 748. | rb-N-107 | TAAATGTTTTATCATTT |
| 749. | rb-N-108 | TCTAAATGTTTTAT |
| 750. | rb-N-109 | TTCTAAATGTTTTAT |
| 751. | rb-N-110 | TAAGATCAAAATAAA |
| 752. | rb-N-111 | ATAAGATCAAAATAAA |
| 753. | rb-N-112 | AATAAGATCAAAATAAA |
| 754. | rb-N-113 | TAATAAGATCAAAATAAA |
| 755. | rb-N-114 | TTAATAAGATCAAAATAAA |
| 756. | rb-N-115 | TTTAATAAGATCAAAATAAA |
| 757. | rb-N-116 | TTGTTTAATAAGAT |
| 758. | rb-N-117 | ATTGTTTAATAAGAT |
| 759. | rb-N-118 | TGATTGTTTAATAA |
| 760. | rb-N-119 | TTGATTGTTTAATAA |
| 761. | rb-N-120 | TTTGATTGTTTAATAA |
| 762. | rb-N-121 | TTTTATAAAACAGT |
| 763. | rb-N-122 | TTTTTATAAAACAGT |
| 764. | rb-N-123 | TTTTTTATAAAACAGT |
| 765. | rb-N-124 | CTTTTTTATAAAACA |
| 766. | rb-N-125 | ACTTTTTTATAAAACA |
| 767. | rb-N-126 | CACCTTTTTTATAAAA |
| 768. | rb-N-127 | ACACTTTTTTATAAAA |
| 769. | rb-N-128 | TACACTTTTTTATAAAA |
| 770. | rb-N-129 | ATACACTTTTTTATAAAA |
| 771. | rb-N-130 | ATTTTGAATTAAAG |
| 772. | rb-N-131 | GATTTTGAATTAA |
| 773. | rb-N-132 | TGATTTTGAATTAA |
| 774. | rb-N-133 | ATGATTTTGAATTAA |
| 775. | rb-N-134 | AATGATTTTGAATTAA |
| 776. | rb-N-135 | ATAATAGAATCATA |
| 777. | rb-N-136 | TATAATAGAATCATA |
| 778. | rb-N-137 | TATAATAGAATCAT |
| 779. | rb-N-138 | TACTATAATAGAAT |
| 780. | rb-N-139 | ATACTATAATAGAAT |
| 781. | rb-N-140 | AATACTATAATAGAAT |
| 782. | rb-N-141 | AGAATACTATAATA |
| 783. | rb-N-142 | TAGAATACTATAATA |
| 784. | rb-N-143 | ATAGAATACTATAATA |

Fig. 3 - 12

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88.21. 17 nt

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| | | |
|------|----------|----------------------------|
| 785. | rb-N-144 | TATAGAATACTATAATA |
| 786. | rb-N-145 | TTATAGAATACTATAATA |
| 787. | rb-N-146 | AATATTGTTTTCA |
| 788. | rb-N-147 | AAATATTGTTTTCA |
| 789. | rb-N-148 | AAAATATTGTTTTCA |
| 790. | rb-N-149 | CAAAATATTGTTTT |
| 791. | rb-N-150 | AAATTTTATATGGA |
| 792. | rb-N-151 | TGAAATTTTATATG |
| 793. | rb-N-152 | CTGAAATTTTATAT |
| 794. | rb-N-153 | TCTGAAATTTTATAT |
| 795. | rb-N-154 | TTCTGAAATTTTATAT |
| 796. | rb-N-155 | ATCTGATTTATTTT |
| 797. | rb-N-156 | AAGATATTAAATGT |
| 798. | rb-N-157 | TGAAGATATTAAAT |
| 799. | rb-N-158 | ATAAATAACAATGA |
| 800. | rb-N-159 | TATAAATAACAATGA |
| 801. | rb-N-160 | GTATAAATAACAAT |
| 802. | rb-N-161 | TGTATAAATAACAAT |
| 803. | rb-N-162 | TTGTATAAATAACAAT |
| 804. | rb-N-163 | TCTTGTATAAATAA |
| 805. | rb-N-164 | ATCTTGTATAAATAA |
| 806. | rb-N-165 | AATCTTGTATAAATAA |
| 807. | rb-N-166 | ACAACTTTTTAAAT |
| 808. | rb-N-167 | TACAACTTTTTAAAT |
| 809. | rb-N-168 | TACAACTTTTTAAAT |
| 810. | rb-T-1 | CGGGGGGTTTTGGGCGGCATG |
| 811. | rb-T-2 | TTTTCGGGGGGTTTTGGGCGGCA |
| 812. | rb-T-3 | TCGGGGGGTTTTGGGCGGC |
| 813. | rb-T-4 | GGTGGCGGCCGTTTTTCGGGGGGT |
| 814. | rb-T-5 | CCGGGGGTTCGCGGCGGCAGCG |
| 815. | rb-T-6 | CGGGGGTTCCGCGGCGG |
| 816. | rb-T-7 | GGCGGCGGTGCCGGGGTTCCGC |
| 817. | rb-T-8 | GGAGGGGGCGGCGGCGGCGGTG |
| 818. | rb-T-9 | GGGGGCGGCGGCGGCGG |
| 819. | rb-T-10 | GGGGCGGCGGCGGCGG |
| 820. | rb-T-11 | AGGGGGCCTGGTGAAG |
| 821. | rb-T-12 | TAGGGGGCCTGGTG |
| 822. | rb-T-13 | GTAGGGGGCCTGGT |
| 823. | rb-T-14 | GAGGTATTGGTGACAAGGTAGGGGGC |
| 824. | rb-T-15 | TCTTCAGGGGTGAAATATAGATGTTT |
| 825. | rb-T-16 | GGACTCTTCAGGGGTG |

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826 TCGGACTATA CTGC
827 CAGTTCGGAC TATACT
828 AAGCCTAAGA CGCA
829 GCCCAAGTTC AACA
830 TGAAAAGTCG CGGT
831 GGTTAATTAA GATGCCTC
832 TCTCTAAGAG CGCA
833 ACGTGAGGTT AGTTTG
834 CACGTGAGGT TAGT
835 CATAGAACAG TCCG
836 CAGTCATAGA ACAGTC
837 CTTTGCACTC ATAGAACA
838 TGCAGTCATA GAAC
839 GGTCGTTTCC ATCT
840 CATAGAAGGT CGTTTC
841 CGTCATAGAA GGTC
842 CATCGTCATA GAAGG
843 GGACGGGAGG AACGAGGCGT TGAG
844 TAGCCATAAG GTCC
845 GGTTACTGTA GCCA
846 GGTTACTGTA GCCA
847 AGTTCTTGCC GCGGAGGT
848 AGGTGAGGAG GTCCGAGT
849 TGGACTGGAT TATCAG
850 GTGGTGGTGA TGTGCCCG
851 TGTCACGTTC TTGG
852 CTCATCTGTC ACGT
853 CGAAGCCCTC GGCGAACC
854 GCGTGTTCTG GCTGTGCAGT TCGG
855 CTGCCCCGTT GACC
856 AGGTTTGCGT AGAC
857 GGTTGAAGTT GCTG
858 CTGGGTTGAA GTTG
859 TGCTGCACGG GCATCTGCTG
860 GGCACGTCT GAGGCTCCTC CTTCAGG
861 ACTCCATGTC GATG
862 CTCTCCGCCT TGATCC
863 GTTCCTCATG CGCTTC
864 CTGAGCTTTC AAGG
865 GCGATTCTCT CCAGCTTCCT TTTTCG
866 CTGAGCTTTC AAGGTTTCA CTTTTTCCTC
867 TCCCTGAGCA TGTT
868 TCTGTTTAAG CTGTGC
869 CTTTCTGTTT AAGCTGTG
870 GGTTTCATGAC TTTCTG
871 CGTGGTTCAT GACT
872 ACTGTTAACG TGGTTC
873 CCACTGTAA CGTG
874 CCCACTGTTA ACGT
875 AGCATGAGTT GGCA
876 GCGTTAGCAT GAGT
877 GTTTGCAACT GCTG
878 CAAAATGTTT GCAACTGC

Fig. 4 - 1

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| | | |
|-----|-------------|-----------------------|
| 879 | TCCATTTTAG | TGCACATC |
| 880 | CTGTTCCATT | TTAGTGCA |
| 881 | GTGTATGAGT | CGTC |
| 882 | CTGTGTATGA | GTCG |
| 883 | CGTAGCTGTG | TATG |
| 884 | TCGTGTAGAG | AGAG |
| 885 | AGTTTGTAGT | CGTGTA |
| 886 | GTTTGTAGTC | GTGTAG |
| 887 | AGTTTGTAGT | CGTG |
| 888 | GGAGTTTGTA | GTCG |
| 889 | TCAGGAGTTT | GTAGTC |
| 890 | GTTTCAGGAG | TTGTAGT |
| 891 | TCGGTTTCAG | GAGT |
| 892 | TTGAGACTCC | GGTA |
| 893 | ACCAGAAAAG | TAGCTG |
| 894 | CCTGACCAGA | AAAG |
| 895 | ATTCAGGCGT | TCCA |
| 896 | GGTAAAAGTA | CTGTCC |
| 897 | GGGTAAAAGT | ACTGTC |
| 898 | GCACCTCCAC | CGCTGCCA |
| 899 | CTCCTGCTCC | TCGGTGAC |
| 900 | GCTTTGACAA | AGCC |
| 901 | CTTGTGCAGA | TCGT |
| 902 | TCATCTTGTG | CAGATC |
| 903 | GTTTCATCTG | TGCAGA |
| 904 | CGTGGTTCAT | CTTG |
| 905 | TCACGTGGTT | CATC |
| 906 | GGTTGGTGTA | AACG |
| 907 | TACGAGCTCC | CGGTCCCGAC |
| 908 | TAGCTGATGG | TGGT |
| 909 | TCCTTGAAGG | TGGA |
| 910 | TCTTCCATGT | TGATGG |
| 911 | CTTTGATGCG | CTCT |
| 912 | CTCCACTTTG | ATGC |
| 913 | GCTCCAGCTT | CGCTTCCGG CACTTGGTGG |
| 914 | GGCCTTGAGC | GTCTTCACCT TGTCCTCCAG |
| 915 | TGACCTTCTG | TTTGAG |
| 916 | CATGACCTTC | TGTTTG |
| 917 | GTCATGACCT | TCTG |
| 918 | CGAGAACATC | ATCG |
| 919 | GTAGTCTGCG | TTGA |
| 920 | GCTGCAGCGG | GAGGATGACG |
| 921 | AGTAAGAGAG | GCTATC |
| 922 | GTAGTAAGAG | AGGC |
| 923 | GGTAGTAAGA | GAGG |
| 924 | GTGAGTG GTA | GTAAGA |
| 925 | GTCCGTGCAG | AAGTCCTG |
| 926 | GAATGAAGTT | GGCACT |
| 927 | GGAATGAAGT | TGGC |
| 928 | GGGAATGAAG | TTGG |
| 929 | GCTGCACCAG | CCACTGCAGG TCCGGACTGG |
| 930 | TCATGGTCTT | CACAAC |
| 931 | CAATGCTCTG | CGCTCGGCCT CCTGTCATGG |

Fig. 4 - 2

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| | | |
|-----|-------------|-----------------------|
| 932 | CTAGAGTTCC | TCAC |
| 933 | GAGTACGCTA | GAGT |
| 934 | GAAGAGTACG | CTAG |
| 935 | CTGCTTCCCA | CCCAGCCCC ACATTCCC |
| 936 | TTCATCCTCT | GTACTGGGCT |
| 937 | GTTACGGATG | TGCA |
| 938 | CAGTTACGGA | TGTG |
| 939 | CCAGTTACGG | ATGT |
| 940 | AGAGTCTGAG | TTGG |
| 941 | GTGAGACTCA | GAGT |
| 942 | TCTTAGGGTG | AGAC |
| 943 | GAGAGTACTT | CTTAGG |
| 944 | GGAAGAACT | ATGAGAGT |
| 945 | CTTAGGGAAG | AAACTATG |
| 946 | CGGTAAGAAA | CTTAGG |
| 947 | AGCATGCGGT | AAGA |
| 948 | GTCTGAAAGC | ATGC |
| 949 | AGAACAAAGA | AGAGCC |
| 950 | CAAGAGAACA | AAGAAGAG |
| 951 | CAGCAAGAGA | ACAAAG |
| 952 | TCCTCAGCAA | GAGA |
| 953 | AGGTGTGACT | TGCA |
| 954 | GAATAGGTGT | GACTTG |
| 955 | CAGAATAGGT | GTGACT |
| 956 | GCAGAATAGG | TGTG |
| 957 | CAGTTGCAGA | ATAGGT |
| 958 | GAAACCATTT | CTGACC |
| 959 | TGTGAAACCA | TTTCTGAC |
| 960 | CACTGTGAAA | CCATTTCT |
| 961 | CCACTGTGAA | ACCA |
| 962 | AGAACTGGCT | CCTGCAGCTT CCCTGCTTCC |
| 963 | CACCTCCATT | CACCC |
| 964 | CAGTAAAAGT | GTCTGC |
| 965 | CGACATTTCAG | TAAAAGTG |
| 966 | GACCGACATT | CAGT |
| 967 | CTTCTGGAGA | TAACTAGA |
| 968 | CATCTTATTC | CTTTCCCT |
| 969 | CAGCCATCTT | ATTCTT |
| 970 | TGCAGCCATC | TTATTC |
| 971 | GAGTGTATCA | GTCAG |
| 972 | GGAGTGTATC | AGTC |
| 973 | CTTGGAGTGT | ATCAGT |
| 974 | ACAGAGTACC | TACC |
| 975 | CCAACCTTCC | CTTAAG |
| 976 | CCTTATGCTC | AATCTC |
| 977 | GTCTTACTCA | AGGG |
| 978 | ACAGTCTTAC | TCAAGG |
| 979 | CATAAGACAC | AGTCTTAC |
| 980 | GAAAGCATAA | GACACAGT |
| 981 | GGAAAGCATA | AGACAC |
| 982 | AGGGATAAAG | GAAAGC |
| 983 | CCTGTATACA | GAGG |
| 984 | TGTCTCCTGT | ATACAG |

Fig. 4 - 3

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| | |
|------|---------------------|
| 985 | CATCTTCTAG TTGGTC |
| 986 | CTCATCTTCT AGTTGG |
| 987 | CTTCTCATCT TCTAGTTG |
| 988 | CAAAGCAGAC TTCTCA |
| 989 | CTGCAAAGCA GACT |
| 990 | CTAGTTTTTC CTTCTCCT |
| 991 | TCTAGTTTTT CCTTCTCC |
| 992 | CAGGATGAAC TCTAGT |
| 993 | TCGTAGAAGG TCGT |
| 994 | AGGGTTACTG TAGC |
| 995 | GTAGTGGTGA TGTG |
| 996 | CGTCGTAGAA GGTC |
| 997 | TTTCGTGCAC ATCC |
| 998 | AGTTTGTAGT CGTGAAGA |
| 999 | CGAGAACATC ATGG |
| 1000 | GTAGTAGGAA AGGC |
| 1001 | GGTAGTAGGA AAGG |
| 1002 | GGAATGGTAG TAGG |
| 1003 | GGTCATTGAG AAGAG |
| 1004 | GCTAATGTTT TTGACC |
| 1005 | GCCAAGGTCCTCAT |
| 1006 | GGAGTCTATCTCCA |
| 1007 | CCAAAGAATCCTGACT |
| 1008 | CACATGCTTAGTGG |
| 1009 | CTCGTAAATGACCG |
| 1010 | AGGAATCTCGTAAATGAC |
| 1011 | CAGCAGCGATTTCAT |
| 1012 | GGAGATCATCAAAGGA |
| 1013 | CTCAGCAATGGTCA |
| 1014 | GATCTCGAACACCT |
| 1015 | CACAATCTCGATCTTTCT |
| 1016 | CTTCTTAAAGATTGGCT |
| 1017 | CACATACCAACTGG |
| 1018 | AGCTTGATGTGAGG |
| 1019 | GAAGTTGTAGCTTGATGT |
| 1020 | GCTTGAAGTTGTAGCT |
| 1021 | CTGCTTGAAGTTGTAG |
| 1022 | GACACAACCTCCTCT |
| 1023 | TCCTTTGATAGACACAAC |
| 1024 | CTCGTTTGATAGACAC |
| 1025 | GGTAGCACACACT |
| 1026 | GGTAACGGTTAGCA |
| 1027 | CGTAACACATTAGAAGC |
| 1028 | CTCATCCGTAAACAC |
| 1029 | CCGGTAAGTATTGTAGTT |
| 1030 | GGTGTATTTCTTGAC |
| 1031 | ACATACCAACTGGTGT |
| 1032 | GTCCTTATACGAAC |
| 1033 | TTCATGTCTG TGCC |
| 1034 | GTAGGTGAGT TCCA |
| 1035 | GTTGTGAGCG ATGA |
| 1036 | CATAGTTGTC CTCAAAGA |
| 1037 | GGCATAGTTG TCCT |

Fig. 4 - 4

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| | |
|------|---------------------|
| 1038 | CATTGTCTAG CACG |
| 1039 | CTCCATTGTC TAGC |
| 1040 | GTATTGTTCA GCGG |
| 1041 | TCAAGATCTC TGTGAG |
| 1042 | CACAAAATCG TGTCTT |
| 1043 | TCCTTCCACA AAATCG |
| 1044 | GTGGAAGATG TCCT |
| 1045 | TCTTGTGGAA GATGTC |
| 1046 | TCTATCAGTG TGAGAG |
| 1047 | GGTTGGTGTC TATC |
| 1048 | ACATCGGAGA ACAG |
| 1049 | CCTTACACAT CGGA |
| 1050 | ACAATCCTCA GAACTC |
| 1051 | GCTCTGACAA TCCT |
| 1052 | TGGTTGAAGT GGAG |
| 1053 | CTGTGGTTGA AGTG |
| 1054 | GTTGTAGGTG ACCA |
| 1055 | CTGTGTTGTA GGTG |
| 1056 | GACTCAAACG TGTC |
| 1057 | CATGGACTCA AACG |
| 1058 | CGAATGTATA CCGG |
| 1059 | CCGAATGTAT ACCG |
| 1060 | GCCGAATGTA TACC |
| 1061 | GTAGTTGTAG GGAC |
| 1062 | TAGAAAGGTA GTTGTAGG |
| 1063 | GTAGAAAGGT AGTTGTAG |
| 1064 | CGTAGAAAGG TAGTTG |
| 1065 | CCGTAGAAAG GTAG |
| 1066 | GACCATAGCA CACT |
| 1067 | GGATATTGGC ACTG |
| 1068 | CCTGGATATT GGCA |
| 1069 | GCTCCCAAAG ATCT |
| 1070 | CCCATCAAAG CTCT |
| 1071 | CAAACACTTG GAGC |
| 1072 | GTCTCAAACA CTTGGA |
| 1073 | GAGTCTCAA CACTTG |
| 1074 | GTAACCTGTG ATCTCT |
| 1075 | GGTAACCTGT GATC |
| 1076 | GTATAGGTAA CCTGTG |
| 1077 | TGAGATGTAT AGGTAACC |
| 1078 | TGCTGAGATG TATAGG |
| 1079 | CCATGCTGAG ATGT |
| 1080 | GGATTACTTG CAGG |
| 1081 | TGTTATGGTG GATGAG |
| 1082 | GGTGTATGG TGGG |
| 1083 | GCAGTTGACA CACT |
| 1084 | AGTACTCGGC ATTC |
| 1085 | CATTACATA CTCCCT |
| 1086 | TCCAAAACAG GTCACT |
| 1087 | GGTCCTTATA GTGG |
| 1088 | CAGAATGCCA ACCA |
| 1089 | ACGAGAATGC CAAC |
| 1090 | GATCCCAAAG ACCA |

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| | | |
|------|-------------|----------|
| 1091 | TCGCTTGATG | AGGA |
| 1092 | CATCGTGTAC | TTCC |
| 1093 | GCATCGTGTA | CTTC |
| 1094 | ACTGTGCCAA | AAGC |
| 1095 | CTTGTAGACT | GTGC |
| 1096 | CCCTTGTAGA | CTGT |
| 1097 | TCAACACTTT | GATGGC |
| 1098 | CCCTCAACAC | TTTG |
| 1099 | GTGTTTTCCC | TCAACA |
| 1100 | GTATGCTTCG | TCTAAG |
| 1101 | CGTATGCTTC | GTCT |
| 1102 | CCATCACGTA | TGCT |
| 1103 | GCATAAGCTG | TGTC |
| 1104 | CATGGTCTAA | GAGG |
| 1105 | CAATCTGCAT | ACACCA |
| 1106 | GGCAATCTGC | ATAC |
| 1107 | CTGTCTCGTC | AATG |
| 1108 | CATAACTCCA | CACATC |
| 1109 | AGTCACACCA | TAACTC |
| 1110 | ACAGTCACAC | CATAAC |
| 1111 | CCCCAAAAGT | CATC |
| 1112 | TCGTAAGGTT | TGGC |
| 1113 | GATCCCATCG | TAAG |
| 1114 | CAATGGTGCA | GATG |
| 1115 | GACATCAATG | GTGC |
| 1116 | GTAGACATCA | ATGGTG |
| 1117 | CATGATCATG | TAGACATC |
| 1118 | CCATGATCAT | GTAGAC |
| 1119 | CATTTGACCA | TGATCATG |
| 1120 | CCAACATTTG | ACCATG |
| 1121 | TCATCCAACA | TTTGACCA |
| 1122 | GAGTCAATCA | TCCAACAT |
| 1123 | CAGAGTCAAT | CATCCA |
| 1124 | CCGACATTCA | GAGT |
| 1125 | GAATTCAGAC | ACCAAC |
| 1126 | GATGACCACA | AAGC |
| 1127 | CCATCAAATA | CATCGG |
| 1128 | TCACCATCAA | ATACATCG |
| 1129 | CAACGTAGCC | ATCA |
| 1130 | ACGTCTTTGA | CGAC |
| 1131 | CAAAAACGTC | TTTGACGA |
| 1132 | GGCAAAAACG | TCTTTG |
| 1133 | CAAAGGCAAA | AACGTC |
| 1134 | GTGTCAAGTA | CTCG |
| 1135 | GTAATAGAGG | TTGTCTG |
| 1136 | CCCAGTAATA | GAGG |
| 1137 | CATGGTGCTC | ACTG |
| 1138 | GTGCCTGTAC | GTAC |
| 1139 | TGCAGGTGGA | TAGT |
| 1140 | CATGTCGATA | GTCTTGCA |
| 1141 | GTCGATAGTC | TTGC |
| 1142 | CCATGTCGAT | AGTC |
| 1143 | CTCCATGTCTG | ATAG |

Fig. 4 - 6

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| | |
|------|---------------------|
| 1144 | CTTGGACAGG ATCT |
| 1145 | TGCTGTTGTA CAGG |
| 1146 | GTGCTGTTGT ACAG |
| 1147 | TTGGCGTAGT AGTC |
| 1148 | TCCACCATTA GCAC |
| 1149 | GATTTTCGTTG TGGG |
| 1150 | GTCATAGATT TCGTTGTG |
| 1151 | TGTA CTCTGC TTGAAC |
| 1152 | GTGTACTCTG CTTG |
| 1153 | TGCTGTGTGT ACTC |
| 1154 | CTGATGTGTT GAAGAACA |
| 1155 | CTCTGATGTG TTGAAG |
| 1156 | GCTCTGATGT GTTG |
| 1157 | GAGCTCTGAT GTGT |
| 1158 | CACTTTTAAC TTGAGCCT |
| 1159 | CTCCACTTTT AACTTGAG |
| 1160 | TGCTGTATTT CTGGTACA |
| 1161 | CCAGGAATTG TTGC |
| 1162 | TTGCTGAGGT ATCG |
| 1163 | GATAACCACT CTGG |
| 1164 | CAAAAGATAA CCACTCTG |
| 1165 | CGGTGACATC AAAAG |
| 1166 | CCTCAATTTT CCCT |
| 1167 | GTTATCCCTG CTGT |
| 1168 | GCAAGTGTGT ATCC |
| 1169 | GATGTCCACT TGCA |
| 1170 | TAGTGAACCC GTTG |
| 1171 | TGCCATGAAT GGTG |
| 1172 | GTTTATGCCA TGAATG |
| 1173 | CATGAGAAGC AGGA |
| 1174 | GCTTTGCAGA TGCT |
| 1175 | GAGCTTTGCA GATG |
| 1176 | TAGTTGGTGT CCAG |
| 1177 | CTGAAGCAAT AGTTGG |
| 1178 | AGCTGAAGCA ATAGTTGG |
| 1179 | GGAGCTGAAG CAAT |
| 1180 | CAATGTACAG CTGC |
| 1181 | GGAAGTCAAT GTACAG |
| 1182 | CGGAAGTCAA TGTAC |
| 1183 | GCGGAAGTCA ATGT |
| 1184 | AGTTGGCATG GTAG |
| 1185 | GCAGAAGTTG GCAT |
| 1186 | CTCCAAATGT AGGG |
| 1187 | ACCTTGCTGT ACTG |
| 1188 | TGCTGGTTGT ACAG |
| 1189 | GGTTATGCTG GTTG |
| 1190 | GTAGTACACG ATGG |
| 1191 | CGTAGTACAC GATG |
| 1192 | CACGTAGTAC ACGA |
| 1193 | CATGTTGGAC AGCT |
| 1194 | GCACGATCAT GTTG |
| 1195 | CACACAGTAG TGCA |
| 1196 | GATCAGAAAA GCGC |

Fig. 4 - 7

| | |
|------|-----------------------|
| 1197 | ACCGTGACCA GATG |
| 1198 | GTAGACAGGC TGAG |
| 1199 | TATCGAGTGT GCTG |
| 1200 | TTGCGCATGA ACTG |
| 1201 | TTGCTCAGGA TCTG |
| 1202 | ACTGGTGAGC TTCA |
| 1203 | GCTCAGGATA GTCT |
| 1204 | TGTAGATGGA AATCACCT |
| 1205 | TGGTGCTGTT GTAG |
| 1206 | TTCTCCTGGA GCAA |
| 1207 | TACTCTTCGT CGCT |
| 1208 | CTTGCGTAG TACT |
| 1209 | CGGCATGTCT ATTTTGTA |
| 1210 | CGGGATGGCA TTTT |
| 1211 | CTGTAGAAAG TGGG |
| 1212 | ACAATTCTGA AGTAGGGT |
| 1213 | ATTGCTGAGA CGTCAAAT |
| 1214 | TCTCCATTGC TGAG |
| 1215 | TCACCAAATT GGAAGCAT |
| 1216 | CTCTGAACTC TGCT |
| 1217 | AACGAAAGAC TCTGAACT |
| 1218 | TGGGTTCCTGC AAAC |
| 1219 | CTGGCTTTTG GGTT |
| 1220 | GTTGTTTCAGG CACT |
| 1221 | TCTGATATAG CTCAATCC |
| 1222 | TCTTTGGACT TGAGAATC |
| 1223 | TGGGTGGAG ATGT |
| 1224 | TGCTGTCGAT GTAG |
| 1225 | ACAACTTTGC TGTCGA |
| 1226 | ATTGCGCTTC TGCT |
| 1227 | GAAGGAGAGC CATT |
| 1228 | TCAGTTACAT CGAAGG |
| 1229 | TGAAGCCATT CATGAACA |
| 1230 | TCCTGTCTTT ATGGTG |
| 1231 | AAATCCCAGG TTCC |
| 1232 | GGACAGTGTA AGCTTATT |
| 1233 | GTACAAAAGT GCAGCA |
| 1234 | TAGATGGTAC AAAAGTGC |
| 1235 | CACTTTTATT TGGGATGATG |
| 1236 | GCAAATCTTG CTTCTAGT |
| 1237 | GTGCCATCAA TACC |
| 1238 | GGTATATGTG GAGG |
| 1239 | TCTGATCACC ACTG |
| 1240 | TCCTAGTGGA CTTTATAG |
| 1241 | TTTTTCCTAG TGGACT |
| 1242 | CAATAACATT AGCAGG |
| 1243 | AAGTCTGTAG GAGG |
| 1244 | TCTGTTGTGA CTCAAG |
| 1245 | GTTGGTCTGT TGTG |
| 1246 | CAAAGCACGC TTCT |
| 1247 | TTTCTAAAGC AATAGGCC |
| 1248 | GCAATTATCC TGCACA |
| 1249 | ACGTAGGCAG CAAT |

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| | |
|------|----------------------|
| 1250 | ATCAATGTAA AGTGGACG |
| 1251 | CTAGATCCCT CTTG |
| 1252 | CCATTTCCAC CCTA |
| 1253 | TGGGTTCTGT TATC |
| 1254 | TGGCATTGTA CCCT |
| 1255 | TCCAGCACAG AAGT |
| 1256 | ATAAATACGG GCATGC |
| 1257 | AGTGTCTGAA CTCC |
| 1258 | TGTGCTGAGT GTCT |
| 1259 | ATAAGCTCAG GACC |
| 1260 | AGGAGAAGCA GATG |
| 1261 | AGCAAGGAGA AGCA |
| 1262 | AATCTTGGGA CACG |
| 1263 | TAGAGAAATGG TTAGAGGT |
| 1264 | GTTTTGCCAA TGTAGTAG |
| 1265 | CTTGGGTGTT TTGC |
| 1266 | GCAAGACTTT ACAATC |
| 1267 | GCATTTGCAA GACTTTAC |
| 1268 | TTTAGCTGCA TTGCAAG |
| 1269 | GCCACTTTTC CAAG |
| 1270 | TTGGTCTTGC CACT |
| 1271 | CAGCACACAG TAGT |
| 1272 | CGATAGTCTT GCAG |

1-113

M

1001.

2443-2454

| | | |
|------|-------------|-------------------------------|
| 1273 | TGF-β2-14/1 | 25 / 36 CTTTCACCAAATTGGAAG |
| 1274 | TGF-β2-14/2 | CACCAAATTGGAAGC |
| 1275 | TGF-β2-14/3 | TCACCAAATTGGAAGC |
| 1276 | TGF-β2-15/1 | CTCTGGCTTTTGGG |
| 1277 | TGF-β2-9/1 | CGGCATGTCTATTTTG |
| 1278 | relA-1 | CACTACAGACGAGC |
| 1279 | relA-2 | CGTGCACTACAGACG |
| 1280 | relA-3 | GGAACAGTTCGTCC |
| 1281 | relA-4 | GAACAGTTCGTCCATG |
| 1282 | relA-5 | CCAGAGTTTCGGTTC |
| 1283 | relA-6 | CTAGGACTGGGACAG |
| 1284 | relA-7 | CGCACTTGTAGCG |
| 1285 | relA-8 | CTCGCACTTGTAGC |
| 1286 | relA-9 | GCACTTGTAGC |
| 1287 | relA-10 | GCGCACTGTCCCTG |
| 1288 | relA-11 | CCAGGGAGATGCGC |
| 1289 | relA-12 | GCCGGTGAGGAGG |
| 1290 | relA-13 | CCGGTGAGGAGGG |
| 1291 | relA-14 | CGGTTCACTCGGC |
| 1292 | relA-15 | GAGTTTCGGTTCACTC |
| 1293 | relA-16 | GGCACGATTGTCAAAG |
| 1294 | relA-17 | CAGGCGTCACCCCC |
| 1295 | relA-18 | GCAGGCGTCACCC |
| 1296 | p105/p50-1 | CTCCCTCCTAAGC |
| 1297 | p105/p50-2 | CCCTCCTAAGCGG |
| 1298 | p105/p50-3 | CGAGTCCGCGTTCCG |
| 1299 | p105/p50-4 | CATCTTCTGCCATTC |
| 1300 | p105/p50-5 | GTGTTTTCCCACCAG |
| 1301 | p105/p50-6 | GGTTTTGGTTCACTAG |
| 1302 | p105/p50-7 | GCATCTTCACGTCTCC |
| 1303 | p105/p50-8 | CTTCACGTCTCCTGTC |
| 1304 | p105/p50-9 | GTCACCGCGTAGTC |
| 1305 | p105/p50-10 | CAAATAGGCAAGGTC |
| 1306 | p105/p50-11 | CTTGCAAATAGGCAAG |
| 1307 | p105/p50-12 | TGCTTGCAAATAGG |
| 1308 | p105/p50-13 | CTGCTTGCAAATAGG |
| 1309 | p105/p50-14 | GCAGGTGGATATTT |
| 1310 | p105/p50-15 | CTGCTGTTGGCAG |
| 1311 | p105/p50-16 | CACTAGTTTCCAAGT |
| 1312 | p105/p50-17 | GTTTTGGTTCACTAG |
| 1313 | p105/p50-18 | CTTTGATTTCAGGATAG |

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| | | |
|------|-------------|--------------------|
| 1314 | p105/p50-19 | GCACTTCTTCTTTATCT |
| 1315 | p105/p50-20 | CCAAGTCAGATTTCC |
| 1316 | p105/p50-21 | GTTTCCAAGTCAGATTTC |
| 1317 | p105/p50-22 | GGTTCACTAGTTTCC |
| 1318 | p105/p50-23 | GGTTTTGGTTCACTAG |
| 1319 | p105/p50-24 | CCGAAAAAATTGGGCA |
| 1320 | p105/p50-25 | CCGAAAAAATTGGG |
| 1321 | p105/p50-26 | CTATCCGAAAAAATTGG |
| 1322 | p105/p50-27 | GTTGATAATGTCATCAG |
| 1323 | p105/p50-28 | CTCATGTTGATAATGTC |
| 1324 | p105/p50-29 | CTGTCACCGCGTAG |
| 1325 | p105/p50-30 | CGTCTCCTGTCACCG |
| 1326 | p105/p50-31 | CTTCACGTCTCCTG |
| 1327 | p105/p50-32 | GAGAACTTTATCATGTC |
| 1328 | p105/p50-33 | GCTATATGCAGGG |
| 1329 | p105/p50-34 | CCAGCTGCTATATGCAGG |
| 1330 | p105/p50-35 | AGGCTAAATTTTGCC |
| 1331 | p105/p50-36 | GGCTAAATTTTGCC |
| 1332 | p105/p50-37 | GGCTAAATTTTGCCCTC |
| 1333 | p105/p50-38 | GCAGGCTAAATTTTGCC |
| 1334 | p105/p50-39 | GAGTTACCCAAGCG |
| 1335 | p105/p50-40 | CAGAGTTACCCAAGCG |
| 1336 | p105/p50-41 | CAGAGTTACCCAAG |
| 1337 | p105/p50-42 | ACAGAGTTACCCAAG |
| 1338 | p105/p50-43 | GGTGCAAAACAGAG |
| 1339 | p105/p50-44 | CTAGGTGCAAAACAG |
| 1340 | p105/p50-45 | GAGAACTTTATCATGTCC |
| 1341 | p105/p50-46 | GCTAGATGAATGGC |
| 1342 | p105/p50-47 | GCAAACATGGCAGGC |
| 1343 | p105/p50-48 | CAGCAAACATGGCA |
| 1344 | p105/p50-49 | GCAGCAAACATGGC |
| 1345 | p105/p50-50 | AGCAGCAAACATGG |
| 1346 | p105/p50-51 | CAGCAGCAAACATG |
| 1347 | p105/p50-52 | AGCAGCAGCAAACA |
| 1348 | p105/p50-53 | CAGCAGCAGCAAACA |
| 1349 | p105/p50-54 | CAGCAGCAGCAAAC |
| 1350 | p105/p50-55 | CACCAGCAGCAGCA |
| 1351 | p105/p50-56 | GCATTGACGTCAGC |
| 1352 | p105/p50-57 | GATGTTGTCGTGCTC |
| 1353 | p105/p50-58 | TGAGATGTTGTCGTGCT |
| 1354 | p105/p50-59 | TGAGATGTTGTCGTG |

Fig. 5 - 2

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| | | |
|------|--------------|--------------------|
| 1355 | p105/p50-60 | GCCAATGAGATGTTG |
| 1356 | p105/p50-61 | CTGCCAATGAGATG |
| 1357 | p105/p50-62 | CACATGGGCATCAC |
| 1358 | p105/p50-63 | TGTCCACATGGGCA |
| 1359 | p105/p50-64 | GTACTGTCCACATG |
| 1360 | p105/p50-65 | CAGCTGCTATATGC |
| 1361 | p105/p50-66 | GTTCTCCACCAGGG |
| 1362 | p105/p50-67 | AGTTCTCCACCAGG |
| 1363 | p105/p50-68 | CAAAGTTCTCCACCAG |
| 1364 | p105/p50-69 | CCAAGAGTCATCCAGG |
| 1365 | p105/p50-70 | CCCAAGAGTCATCC |
| 1366 | p105/p50-71 | CCTGCATTTTCCCAAG |
| 1367 | p105/p50-72 | TCCTGCATTTTCCC |
| 1368 | p105/p50-73 | GCCATATCTAGAGGC |
| 1369 | p105/p50-74 | TCACATCTTCAGCC |
| 1370 | p105/p50-75 | GCTTCACATCTTCAGC |
| 1371 | p105/p50-76 | CAGCTTCACATCTTC |
| 1372 | p105/p50-77 | GTAAC TTATACAGCTGC |
| 1373 | p105/p50-78 | CCAGTTTTTGTCTGG |
| 1374 | p105/p50-79 | CCATTTGTCTCAGG |
| 1375 | p105/p50-80 | GTGTAGCCCATTG |
| 1376 | p105/p50-81 | GCTTCGGTGTAGCC |
| 1377 | p105/p50-82 | GATCACTTCAATTGCTTC |
| 1378 | p105/p50-83 | CTTGTGGAGGCAGG |
| 1379 | p105/p50-84 | GCTGCCTTGTGGAG |
| 1380 | p105/p50-85 | CTATTTGCTGCCTTGTGG |
| 1381 | p105/p50-86 | GGATGTCTCCACGC |
| 1382 | p105/p50-87 | GGAAGGATGTCTCC |
| 1383 | p105/p50-88 | TGCGGAAGGATGTC |
| 1384 | p105/p50-89 | GTTTGCGGAAGGATGTC |
| 1385 | p105/p50-90 | GCTGAGTTTGCGGA |
| 1386 | p105/p50-91 | GGTAAAGCTGAGTTTG |
| 1387 | p105/p50-92 | TCGGTAAAGCTGAG |
| 1388 | p105/p50-93 | GACTCGGTAAAGCTG |
| 1389 | p105/p50-94 | AGAGACTCGGTAAAGC |
| 1390 | p105/p50-95 | GAAATTGTCAGCAGGC |
| 1391 | p105/p50-96 | GAAATTGTCAGCAGG |
| 1392 | p105/p50-97 | GGAAATTGTCAGCAGG |
| 1393 | p105/p50-98 | GGAAATTGTCAGCAG |
| 1394 | p105/p50-99 | GGGAAATTGTCAGC |
| 1395 | p105/p50-100 | GTGTGGGAAATTGTC |

Fig. 5 - 3

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| | | |
|------|--------------|-------------------|
| 1396 | p105/p50-101 | GGTTTACACGGTGTG |
| 1397 | p105/p50-102 | GCTTTGGTTTACACG |
| 1398 | p105/p50-103 | GCACCTTTGGGATGC |
| 1399 | NFKB2-1 | CCAGGTTCTGCTTCC |
| 1400 | NFKB2-2 | GCTCTGTCTAGTGGC |
| 1401 | NFKB2-3 | ACTCTCCATGTCTC |
| 1402 | NFKB2-4 | CAACTCTCCATGTCTC |
| 1403 | NFKB2-5 | CAACTCTCCATGTC |
| 1404 | NFKB2-6 | AGCAACTCTCCATG |
| 1405 | NFKB2-7 | GTAGCAACTCTCCATG |
| 1406 | NFKB2-8 | GTAGCAACTCTCCA |
| 1407 | NFKB2-9 | GGTTGTAGCAACTCTCC |
| 1408 | NFKB2-10 | CGGGCAGTCCTCCA |
| 1409 | NFKB2-11 | GCACCGGGCAGTC |
| 1410 | NFKB2-12 | AGGCACCGGGCAG |
| 1411 | NFKB2-13 | GTGTGTTACCAGGTC |
| 1412 | NFKB2-14 | TGTGTGTTACCAGGT |
| 1413 | NFKB2-15 | TGGGTCACTGTGTG |
| 1414 | NFKB2-16 | CAGACTGTGGGCATG |
| 1415 | NFKB2-17 | CCCACCAGACTGTGGG |
| 1416 | NFKB2-18 | CCACCAGACTGTGG |
| 1417 | NFKB2-19 | TGCCCCACCAGACTG |
| 1418 | NFKB2-20 | CGGCTTCCTCCCC |
| 1419 | NFKB2-21 | CCTTGTCTTCCACC |
| 1420 | NFKB2-22 | ACCGAGGCTGCCAC |
| 1421 | NFKB2-23 | GGAAGAAACCGAGG |
| 1422 | NFKB2-24 | GGGAAGAAACCGAG |
| 1423 | NFKB2-25 | GGCCATCTGCGCC |
| 1424 | NFKB2-26 | GCGGCCATCTGCG |
| 1425 | NFKB2-27 | GTGGCGGCCATCTG |
| 1426 | NFKB2-28 | ACCGTGGCGGCCAT |
| 1427 | NFKB2-29 | GCCGCTCAATCTTCATC |
| 1428 | NFKB2-30 | CTTCATCTTGTGATAGG |
| 1429 | NFKB2-31 | GCTCAATCTTCATCTTG |
| 1430 | NFKB2-32 | CAGAAACACTGTTACAG |
| 1431 | NFKB2-33 | CAGTTGCAGAAACACTG |
| 1432 | NFKB2-34 | GTTTCAGTTGCAGAAAC |
| 1433 | NFKB2-35 | CTTCCACCAGAGGG |
| 1434 | NFKB2-36 | GTCTTCCACCAGAG |
| 1435 | NFKB2-37 | CTTGTCTTCCACCAGAG |
| 1436 | NFKB2-38 | TCCTTGTCTTCCAC |

Fig. 5 - 4

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| | | |
|------|----------|-------------------|
| 1437 | NFKB2-39 | CTTCCTTGTCTTCCAC |
| 1438 | NFKB2-40 | CATCTTGTGATAGGG |
| 1439 | NFKB2-41 | GCTAGGTGCAGTGGT |
| 1440 | NFKB2-42 | GATGGCTAGGTGCA |
| 1441 | NFKB2-43 | GTGGATGATGGCTAG |
| 1442 | NFKB2-44 | CCCGTGGATGATGG |
| 1443 | NFKB2-45 | CTGCCCCGTGGATGA |
| 1444 | NFKB2-46 | AGAGCCTCCACCCA |
| 1445 | NFKB2-47 | GTTGTACTCTCGAGC |
| 1446 | NFKB2-48 | CGTTGTACTCTCG |
| 1447 | NFKB2-49 | CGCGTTGTACTCTC |
| 1448 | NFKB2-50 | GAGTCTCCATGCCG |
| 1449 | NFKB2-51 | CTGAGTCTCCATGC |
| 1450 | NFKB2-52 | CATGGCTGAGTCTC |
| 1451 | NFKB2-53 | TGCATGGCTGAGTC |
| 1452 | NFKB2-54 | GCGTTCACGTTGGC |
| 1453 | NFKB2-55 | GTGCGAGCGTTCAC |
| 1454 | NFKB2-56 | AGGTGCGAGCGTTC |
| 1455 | NFKB2-57 | GCAAAGGTGCGAGC |
| 1456 | NFKB2-58 | CCTGGTGGCTCAGG |
| 1457 | NFKB2-59 | GTCAGTCACCTGAG |
| 1458 | NFKB2-60 | CAGGTCAGTCACCTG |
| 1459 | NFKB2-61 | CAGCAGGTCAGTCAC |
| 1460 | NFKB2-62 | GCAGCAGGTCAGTC |
| 1461 | NFKB2-63 | CATTTAGCAGCAAGGTC |
| 1462 | NFKB2-64 | GCAGCATTTAGCAGC |
| 1463 | NFKB2-65 | CTGAGCAGCATTTAG |
| 1464 | NFKB2-66 | CCCATGAGAATCCT |
| 1465 | NFKB2-67 | CCTTCCCATGAGAATCC |
| 1466 | NFKB2-68 | TCCTCCCCTTCCCA |
| 1467 | NFKB2-69 | GCCTCCAGTAGACC |
| 1468 | NFKB2-70 | GTCAGACAGGGCCT |
| 1469 | NFKB2-71 | CCATGTCAGACAGG |
| 1470 | NFKB2-72 | GGCCCATGTCAGAC |
| 1471 | TANK-1 | GCTATTCCTGAAATCAC |
| 1472 | TANK-2 | CCTCTTGTCTTCTTACC |
| 1473 | TANK-3 | GGAGAAGAAACCTCTTG |
| 1474 | TANK-4 | CCTTGCTGAAGTTTCTT |
| 1475 | TANK-5 | CCAAGACTCCTTGC |
| 1476 | TANK-6 | CCCTTTCATGGAGC |
| 1477 | TANK-7 | CCTCTTGGTGTGAC |

Fig. 5 - 5

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| | | |
|------|---------------------|--------------------|
| 1478 | TANK-8 | GACTAAGGATGCCG |
| 1479 | TANK-9 | GTGGCAGGACTAAGG |
| 1480 | TANK-10 | AGACGTGGCAGGAC |
| 1481 | I-kappa-Bepsilon-1 | CTTCCAGCAGGCAG |
| 1482 | I-kappa-Bepsilon-2 | GTTCTCTGCCTGG |
| 1483 | I-kappa-Bepsilon-3 | GATGTTCTCTGCCTG |
| 1484 | I-kappa-Bepsilon-4 | GAGATGTTCTCTGCC |
| 1485 | I-kappa-Bepsilon-5 | GTGAGATGTTCTCTG |
| 1486 | I-kappa-Bepsilon-6 | CAGAGAGTGAGATGTTCC |
| 1487 | I-kappa-Bepsilon-7 | CCAGAGAGTGAGATGTTC |
| 1488 | I-kappa-Bepsilon-8 | GGTCCAGAGAGTGAG |
| 1489 | I-kappa-Bepsilon-9 | GAGGTCCAGAGAGTG |
| 1490 | I-kappa-Bepsilon-10 | GGTCTGTAGTGCC |
| 1491 | TRAF-6-1 | GATTTTATGATGCAGGC |
| 1492 | TRAF-6-2 | GACCTGCATCCCTTATTG |
| 1493 | TRAF-6-3 | TAGTTGATTTTCCAGCAG |
| 1494 | TRAF-6-4 | GAATCTCACGTTTTGC |
| 1495 | TRAF-6-5 | CAGAGAAAGAATCTCACG |
| 1496 | TRAF-6-6 | TTTACCATCAGAGAAAG |
| 1497 | TRAF-6-7 | CATTTGGACATTTACC |
| 1498 | TRAF-6-8 | CCTTCATTTGGACATTTT |
| 1499 | TRAF-6-9 | CAATGTGCTTGATGATCC |
| 1500 | Rank-1 | CGCATCGGATTTCTC |
| 1501 | Rank-2 | CAAACCGCATCGGATTTT |
| 1502 | Rank-3 | GAACTGCAAACCGC |
| 1503 | Rank-4 | GCAGAGAAGAACTGC |
| 1504 | Rank-5 | GCAAGTAAACATGGG |
| 1505 | Rank-6 | GGTCCACGTTTTGG |
| 1506 | Rank-7 | GCAAGGGTCCACGTTT |
| 1507 | Rank-8 | TGGCTTCTTCTTCAGGG |
| 1508 | Rank-9 | TCCTGCTGGCTTCTTC |
| 1509 | Rank-10 | GTCTGCTGGCTTC |
| 1510 | IL-5-1 | GGTAGTCTAGGAATTGG |
| 1511 | IL-5-2 | CTTGCAGGTAGTCTAGG |
| 1512 | IL-5-3 | GAAACTCTTGCAGGTAG |
| 1513 | IL-5-4 | CACCAAGAACTCTTGC |
| 1514 | IL-5-5 | CATTACACCAAGAACTC |
| 1515 | IL-5-6 | CTCGGTGTTTATTACACC |
| 1516 | IL-5-7 | CTTTCTATTATCCACTCG |
| 1517 | IL-5-8 | CCAGTTTAGTCTCAACTT |
| 1518 | IL-5-9 | AACCAGTTTAGTCTCAAC |

Fig. 5 - 6

| | | |
|------|-----------------------|-----------------------|
| 1519 | IL-5-10 | ACAAACCAGTTTGTCTC |
| 1520 | IL-13-1 | CTCGCGAAAAAGTTTCTT |
| 1521 | IL-13-2 | CCCTCGCGAAAAAGTTTC |
| 1522 | IL-13-3 | GTCCCTCGCGAAAAAG |
| 1523 | IL-13-4 | CAGTTGAACCGTCCC |
| 1524 | IL-13-5 | GCTTTCGAAGTTTCAGTT |
| 1525 | IL-13-6 | GATGCTTTCGAAGTTTC |
| 1526 | IL-13-7 | CTGTCTCTGCAAATAATG |
| 1527 | IL-15-1 | CAC TTATTACATTCACCC |
| 1528 | IL-15-2 | TTTTCCTCCAGTTCCTC |
| 1529 | IL-15-3 | GGACAATATGTACAAAAC TC |
| 1530 | IL-15-4 | GTTGATGAACATTTGGAC |
| 1531 | IL-15-5 | GTGTTGATGAACATTTGG |
| 1532 | I-kappaB(newmember)-1 | CAAAATTTGGCCAGGG |
| 1533 | I-kappaB(newmember)-2 | GCCCCAAAATTTGGCC |
| 1534 | I-kappaB(newmember)-3 | CCCAGCCCCAAAATTTGG |
| 1535 | I-kappaB(newmember)-4 | GTCCCCAGCCCCAAAATT |
| 1536 | I-kappaB(newmember)-5 | AAATCGCCAGAGGCTG |
| 1537 | I-kappaB(newmember)-6 | ACCAAATCGCCAGAGG |
| 1538 | I-kappaB(newmember)-7 | CATCACCAAATCGCCAG |
| 1539 | Prostaglan.Rec.EP3-1 | TAGGAGTGGTTGAGGC |
| 1540 | Prostaglan.Rec.EP3-2 | GTGTAGGAGTGGTTGAG |
| 1541 | Prostaglan.Rec.EP3-3 | CTGTGTAGGAGTGG |
| 1542 | Prostaglan.Rec.EP3-4 | CCCACATGCCTGTG |
| 1543 | Prostaglan.Rec.EP3-5 | CGATGAACAACGAG |
| 1544 | Prostaglan.Rec.EP3-6 | CTGGCGATGAACAACG |
| 1545 | Prostaglan.Rec.EP3-7 | CGCTGGCGATGAAC |
| 1546 | Prostaglan.Rec.EP3-8 | GAGCTAGTCCCGTTG |
| 1547 | Prostaglan.Rec.EP3-9 | GCGAAGAGCTAGTCC |
| 1548 | Prostaglan.Rec.EP3-10 | CCAGTTATGCGAAGAGC |
| 1549 | Prostaglan.Rec.EP3-11 | CCCCAGTTATGCGAAG |
| 1550 | PresenilinI-1 | CACATGCTTGGCGC |
| 1551 | PresenilinI-2 | GATCACATGCTTGGCG |
| 1552 | PresenilinI-3 | GACAAAGAGCATGATCAC |
| 1553 | PresenilinI-4 | GAGTCACAGGGACAAAG |
| 1554 | PresenilinI-5 | GAGAGTCACAGGGAC |
| 1555 | PresenilinI-6 | GCAGAGAGTCACAGG |
| 1556 | PresenilinI-7 | CCATGCAGAGAGTC |
| 1557 | PresenilinI-8 | CCACCATGCAGAGAG |
| 1558 | PresenilinI-9 | TAGCCACGACCACC |
| 1559 | PresenilinI-10 | GATTAGCTGCCCATCCTT |

Fig. 5 - 7

| | | |
|------|----------------|--------------------|
| 1560 | PresenilinI-11 | GGTATAGATTAGCTGCC |
| 1561 | PresenilinI-12 | GTATCTTCTGTGAATGGG |
| 1562 | PresenilinI-13 | CTGGCCCACAGTCT |
| 1563 | PresenilinI-14 | CTCTGGCCCACAGT |
| 1564 | PresenilinI-15 | TGCAGGGCTCTCTG |
| 1565 | PresenilinI-16 | AGTGCAGGGCTCTC |
| 1566 | PresenilinI-17 | CACTGATCATGATGGC |
| 1567 | PresenilinI-18 | GACACTGATCATGATGGC |
| 1568 | PresenilinI-19 | ACAATGACACTGATCATG |
| 1569 | PresenilinI-20 | GAACCACCAGGAGGAT |
| 1570 | PresenilinI-21 | GACACAAAACAGCCACT |
| 1571 | PresenilinI-22 | GTGGACCTTTCGGAC |
| 1572 | PresenilinI-23 | CAACCAGCATACGAAGT |
| 1573 | PresenilinI-24 | TCCCTCTGGGCTTC |
| 1574 | PresenilinI-25 | ACTGTCCCTCTGGG |
| 1575 | PresenilinI-26 | GACTGTCCCTCTGG |
| 1576 | PresenilinI-27 | CCTAGATGACTGTCCC |
| 1577 | PresenilinI-28 | CAGCGAGGATACTGC |
| 1578 | PresenilinI-29 | CTTCACCAGCGAGGAT |
| 1579 | PresenilinI-30 | TTTCCTCTGGGTCTTCAC |
| 1580 | PresenilinI-31 | CTTTCCTCTGGGTCTTC |
| 1581 | PresenilinI-32 | CTCCCAATCCAAGTTTT |
| 1582 | TRADD-1 | TTCATCCCGGAGCC |
| 1583 | TRADD-2 | TTCTTCATCCCGGAGC |
| 1584 | TRADD-3 | GCTCAGCCAGTTCTTC |
| 1585 | TRADD-4 | GACAGAGAGGGCAC |
| 1586 | TRADD-5 | CTTCACCTCCGACAG |
| 1587 | TRADD-6 | GAAAAGTCTGGGCAGG |
| 1588 | TRADD-7 | GACCCTGGAACAGAAAAG |
| 1589 | TRADD-8 | CTGACCCTGGAACAG |
| 1590 | TRADD-9 | ACTACAGGCTGACCCT |
| 1591 | TRADD-10 | ATTCACTACAGGCTGACC |
| 1592 | TRADD-11 | CGATTCACTACAGG |
| 1593 | TRADD-12 | GGCCGATTCACTAC |
| 1594 | TRADD-13 | CGAACGTCTGTTGGTC |
| 1595 | TRADD-14 | CGCGAACGTCTGTTG |
| 1596 | PKA-1 | CTTCTGTTTGTGAGGAT |
| 1597 | PKA-2 | TTCACCACCTTCTGTTG |
| 1598 | PKA-3 | AGGATGCGCTTTTCATTC |
| 1599 | PKA-4 | AGCTTGCAGGATGCG |
| 1600 | PKA-5 | GTTGACAGCTTGCAGGAT |

| | | |
|------|---------------|--------------------|
| 1601 | PKA-6 | GGAACGGAAAGTTGACAG |
| 1602 | PKA-7 | AACTCGAGTTTGACGAGG |
| 1603 | PKA-8 | TGTCCTTGAAGGAGAAC |
| 1604 | PKA-9 | CGTACTCCATGACCATGT |
| 1605 | PKA-10 | GCACGTACTCCATGAC |
| 1606 | PKA-11 | GATTCTCCGGCTTCAG |
| 1607 | PKA-12 | TCAATGAGCAGATTCTCC |
| 1608 | PKA-13 | GGTCAATGAGCAGATTC |
| 1609 | PKA-14 | CCCTGCTGGTCAATG |
| 1610 | PKA-15 | TAGCCCTGCTGGTC |
| 1611 | PKA-16 | CGCTTGGCGAAACC |
| 1612 | PKA-17 | CCTTCACGCGCTTG |
| 1613 | PKA-18 | AAGGTCCAAGTGCG |
| 1614 | PKA-19 | TGCCGCACAAGGTC |
| 1615 | IL-12alpha-1 | GGTGAGGACCACCATT |
| 1616 | IL-12alpha-2 | GGGTGTCACAGGTG |
| 1617 | IL-12alpha-3 | ATACCATCTTCTTCAGGG |
| 1618 | IL-12alpha-4 | GGTGATACCATCTTCTTC |
| 1619 | IL-12alpha-5 | CCAGGTGATACCATCTTC |
| 1620 | IL-12alpha-6 | CCTCACTGCTCTGGT |
| 1621 | IL-12alpha-7 | TAAGACCTCACTGC |
| 1622 | IL-12alpha-8 | CAGAGCCTAAGACCTC |
| 1623 | IL-12alpha-9 | CCAGAGCCTAAGACC |
| 1624 | IL-12alpha-10 | TCTTCCTTTTTGTGAAGC |
| 1625 | IL-12alpha-11 | GACCAAATTCATCTTCC |
| 1626 | IL-12alpha-12 | ATCAGTGGACCAAATTC |
| 1627 | IL-12alpha-13 | GGTTCTTTCTGGTCCTTT |
| 1628 | IL-12alpha-14 | TTTTTGGGTTCTTTCTGG |
| 1629 | IL-12alpha-15 | GGTCTTATTTTTGGGTTT |
| 1630 | IL-12alpha-16 | AATGGGCAGACTCTCCT |
| 1631 | IL-12alpha-17 | TCCACCATGACCTCAATG |
| 1632 | IL-12alpha-18 | AACGGCATCCACCATG |
| 1633 | IL-12alpha-19 | GTGAACGGCATCCAC |
| 1634 | IL-12alpha-20 | ACTTGAGCTTGTGAACGG |
| 1635 | IL-12alpha-21 | TTCATACTTGAGCTTGTG |
| 1636 | IL-12alpha-22 | CTGGTGTAGTTTTCATAC |
| 1637 | IL-12alpha-23 | AGCTGCTGGTGTAGTTTT |
| 1638 | IL-12beta-1 | AGGAGGACCAGGGT |
| 1639 | IL-12beta-2 | AGGTGGTCCAGGAG |
| 1640 | IL-12beta-3 | TTTCTGGCCAAACTGAGG |
| 1641 | IL-12beta-4 | GGAGGTTTCTGGCC |

| | | |
|------|--------------|--------------------|
| 1642 | IL-12beta-5 | TCTGGAGTGGCCAC |
| 1643 | IL-12beta-6 | CTTCTGGAGCATGTTGCT |
| 1644 | IL-12beta-7 | GCCTTCTGGAGCATG |
| 1645 | IL-12beta-8 | GTTTGTCTGGCCTTCTG |
| 1646 | IL-12beta-9 | GAGTTTGTCTGGCCTTCT |
| 1647 | IL-12beta-10 | CTAGAGTTTGTCTGGCCT |
| 1648 | IL-12beta-11 | GCAAGGGTAAAATTCTAG |
| 1649 | IL-12beta-12 | AGTGCAAGGGTAAAATTC |
| 1650 | IL-12beta-13 | AAACAGGCCTCCACT |
| 1651 | IL-12beta-14 | CTTGGTTAATTCCAATGG |
| 1652 | IL-12beta-15 | AGGCAACTCCCATTAGTT |
| 1653 | IL-12beta-16 | TACTACTAAGGCACAGGG |
| 1654 | IL-12beta-17 | AATACTACTAAGGCACAG |
| 1655 | IL-12beta-18 | GTACATCTTCAAGTCTTC |
| 1656 | Pg-R | GGAGTGGACATGAT |
| 1657 | thr | AAGAAGATGAAGCCTTTG |
| 1658 | ref-fosjun | CCGTCTTACTCTTCTTGG |
| 1659 | PIV | CCGATACAATTCCAAGG |
| 1660 | PIV | CCTTTTCCTTCTGAG |
| 1661 | PIV | CTGTTGCAAGTACG |
| 1662 | bak | CAGAAGCAGAGGGC |
| 1663 | bak | CCTCAGAAGCAGAGG |
| 1664 | bak | CTCCTCAGAAGCAG |
| 1665 | bak | ACAGGCTGGTGGCA |
| 1666 | bak | CCACTCTCAAACAGGC |
| 1667 | bak | ACGGTAGCCGAAGC |
| 1668 | bak | GACGGTAGCCGAAGC |
| 1669 | bak | GGCCAGACGGTAGC |
| 1670 | bak | GTGTAGGGCCAGACGGTA |
| 1671 | bak | CCGAAGCCATTTTTCAGG |
| 1672 | bak | CCCCGAAGCCATTTTTC |
| 1673 | bak | GGTTGATGTCGTCC |
| 1674 | bax | GCTTGAGACACTCGC |
| 1675 | bax | CCGGACCCGTCCAT |
| 1676 | bclx | GCTTGCTTTACTGC |
| 1677 | bclx | GGTTGCTCTGAGAC |
| 1678 | bclx | GCCACAGTCATGCC |
| 1679 | bmp | CGGGCATGCTGGCG |
| 1680 | bmp | GTGAAGTTCAGGATGATC |
| 1681 | bmp | CCAGTGCCTCATGG |
| 1682 | ICE | CAGTGTTCTCCATGG |

Fig. 5 - 10

| | | |
|------|--------|-------------------|
| 1683 | ICE | CTGTACCAGACCGAG |
| 1684 | ICE | GCATACTGTTTCAGC |
| 1685 | ich | GCCATCAGCTCCTTG |
| 1686 | ich | CCACACCATAGATGG |
| 1687 | ich | GCTGGAGCAGTTTCC |
| 1688 | bcl1 | CTCGCTTCTGCTGC |
| 1689 | bcl2 | ACCGTGGCAAAGCG |
| 1690 | mucrep | AGGTGACACCGTGG |
| 1691 | AHR | GACTTGATTCCTTCAG |
| 1692 | AHR | GGATTTGACTTGATTCC |
| 1693 | AHR | GCTGCTGTTTCATGG |
| 1694 | AHR | CCGTTTCTTTCAGTAGG |
| 1695 | CD2 | CTTGAAGTAGGAGC |
| 1696 | MEK2 | CGCTCCTACATGGC |
| 1697 | tnf | GATGAGGTACAGGCC |
| 1698 | tnf | GTAGATGAGGTACAG |
| 1699 | tnf | GAGTAGATGAGGTAC |
| 1700 | tnf | CCTGGGAGTAGATG |
| 1701 | tnf | GGACCTGGGAGTAG |
| 1702 | tnf | ACATGGGTGGAGGG |
| 1703 | tnf | GTGCTCATGGTGTC |
| 1704 | tnf | CTTTCAGTGCTCATG |
| 1705 | tnf | TGCTTTCAGTGCTCA |
| 1706 | tnf | GATGATCTGACTGCC |
| 1707 | tnf | GTTCGAGAAGATGATC |
| 1708 | tnf | GGGTTTCGAGAAGATG |
| 1709 | tnf | GGTTTGCTACAACATG |
| 1710 | tnf | CAGCTTGAGGGTTTG |
| 1711 | tnf | TGCCCCCTCAGCTTG |
| 1712 | TNFR | GACACACACTATCTC |
| 1713 | IL-18 | GCAGCCATCTTTATTC |
| 1714 | IL-18 | G TTCAGCAGCCATC |
| 1715 | IL-18 | TGGTTCAGCAGCCA |
| 1716 | IL-18 | CTACTGGTTCAGCAGC |
| 1717 | IL-18 | TCTACTGGTTCAGC |
| 1718 | IL-18 | GCCACAAAGTTGATGC |
| 1719 | IL-18 | CATTGCCACAAAGTTG |
| 1720 | IL-18 | GAGAACTTGGTCATTC |
| 1721 | IL-18 | GGTCAATGAAGAGAAC |
| 1722 | IL-18 | CGATTTCCCTTGGTC |
| 1723 | IL-18 | CCGATTTCCCTTGGTC |

Fig. 5 - 11

| | | |
|------|-----------------|--------------------|
| 1724 | IL-18 | CAAATAGAGGCCGATTTC |
| 1725 | IL-18 | CAAATAGAGGCCGA |
| 1726 | IL-18 | CCTCTAGGCTGGCT |
| 1727 | IL-18 | CATACCTCTAGGCTG |
| 1728 | IL-18 | AGCCATACCTCTAG |
| 1729 | IL-18 | CAGCCATACCTCTAG |
| 1730 | IL-18 | CACAGAGATAGTTACAG |
| 1731 | IL-18 | GTCTTCGTTTTGAACAG |
| 1732 | IL-18 | CTAGTCTTCGTTTTGAAC |
| 1733 | IL-18 | TAGCTAGTCTTCGTTTTG |
| 1734 | IL-18 | GAGCCACTGCGCC |
| 1735 | IL-18 | CGTGAGCCACTGCG |
| 1736 | IL-12-Rec | CGTAACGATCACTGG |
| 1737 | IL-12-Rec | GCACTCGTAACGATC |
| 1738 | IL-12-Rec | GGAGCACTCGTAAC |
| 1739 | IL-12-Rec | CATCATCCTGAGGT |
| 1740 | IL-12-Rec | CAGTATCATCATCCTG |
| 1741 | IL-12-Rec | CTCAGTATCATCATCC |
| 1742 | IL-12-Rec beta2 | CTAAAAGTATGTGCCATC |
| 1743 | IL-12-Rec beta2 | CACATCGCCTCTCT |
| 1744 | IL-12-Rec beta2 | GCTTCACAGTCACATCGC |
| 1745 | IL-12-Rec beta2 | GGAAGGCTTCACAGTC |
| 1746 | IL-12-Rec beta2 | CCTGTGACTTGAGAATTG |
| 1747 | IL-12-Rec beta2 | GGAAGACCTGTGAC |
| 1748 | IL-12-Rec beta2 | CTCTGCTCCACATATTTG |
| 1749 | IL-12-Rec beta2 | CAACGAAGATCTCTG |
| 1750 | IL-12-Rec beta2 | CAACACCAACGAAG |
| 1751 | PKC-beta | GGTCTTCTGTTTGC |
| 1752 | CB-1-Rec | CGATGAAGTGGTAGGAAG |
| 1753 | TGF-alpha | GGTTGCATGGAAGC |
| 1754 | Fascin | GGTCACAAACTTGCC |
| 1755 | p300 | CTGATTTGGTCCACTAG |
| 1756 | CBP | CATGTTAGCACTGTTC |
| 1757 | rac-alpha | GGTCTTGATGTACTCC |
| 1758 | EBV | CCACCTAAAGAGAGATC |
| 1759 | HSPQ | CTTGTA CTGCACCATC |
| 1760 | CC-CKR1 | GCCAGTTAAGAAGATG |
| 1761 | CC-CKR4 | GAGATCATGATCCATGG |
| 1762 | c-CRK | GTAGTGTCCCAATAGTG |
| 1763 | c-CRK | CTTCCTCATCATTCCC |
| 1764 | CRKL | CACAAGCTTTTCGAC |

Fig. 5 - 12